A COMPARISON OF THE PSYCHOLOGICAL EFFECTS OF ACUTE AND CHRONIC ADMINISTRATION OF CHLORPROMAZINE AND SECOBARBITAL (QUINALBARBITONE) IN SCHIZOPHRENIC PATIENTS*

By

CONAN KORNETSKY, Ph.D.
MANSON PETTIT, M.D.
RONALD WYNNE, M.A.

and

EDWARD V. EVARTS, M.D.

Laboratory of Clinical Science
National Institute of Mental Health and St. Elizabeth's Hospital
National Institutes of Health
Public Health Service
U.S. Department of Health, Education and Welfare, Bethesda, Maryland

In two previous studies (3 and 4) certain psychological effects of single doses of chlorpromazine and secobarbital (quinalbarbitone) were studied in young normal subjects. It was found that 100 and 200 mg. of chlorpromazine had a greater effect on tests of motor co-ordination than did 100 and 200 mg. of secobarbital, respectively, and that 200 mg. of secobarbital had a greater effect on a test related to intellectual functioning than did 200 mg. of chlorpromazine. The results in our study of the effects of single doses of chlorpromazine differed from the results of studies of the effects of chronic administration of chlorpromazine by Lehmann and Hanrahan (5) and Shaten et al. (7). These investigators found that chronic administration of chlorpromazine to schizophrenic patients was followed by improvement or only slight impairment in performance on most of the psychological tests used. The differences between the results we have obtained following administration of single doses of chlorpromazine to normal subjects, and the results of Lehmann and Hanrahan and Shaten et al. could be attributed either to differences between the effects of chronic and acute administration of chlorpromazine or to differences in the response between normal subjects and schizophrenic patients.

The purpose of the present study was to shed further light on these drug effects by comparing the response to chronic and acute administration of chlorpromazine and secobarbital in young chronic schizophrenic patients. In addition, the effects of acute administration of these drugs to schizophrenics were compared to the effects in normals observed in the previous study. It was not feasible to study the effects of chronic administration of chlorpromazine to normal subjects.

* This paper was presented in part at the 1958 Meeting of the Federation of American Societies for Experimental Biology.
CHLORPROMAZINE AND SECOBARBITAL IN SCHIZOPHRENIA

METHODS

Twelve male schizophrenic patients were selected from the population of a subacute service of the hospital. Mean age was 30.1 years (range: 21–40); mean years of hospitalization was 3.75 (range: 1–11.5); mean years of schooling was 12.4 (range: 10–16); and mean I.Q. was 99.1 (range: 84–127). No attempt was made to select any single subtype of schizophrenia; the main criteria for selection were co-operativeness, a minimum of one year of hospitalization, and a maximum age of 40 years. With one exception, the same subjects were used in both the acute and chronic studies.

Five of the subjects were receiving chlorpromazine for therapeutic purposes prior to the start of the experiment, and three additional subjects had received chlorpromazine sometime during their hospitalization. All medications were withdrawn from the subjects at least two weeks prior to the start of the experiment.

Acute Study

One hundred and 200 mg. doses of secobarbital sodium, and 100 and 200 mg. of chlorpromazine hydrochloride were administered on separate occasions to each subject. Each drug at each dose was given twice so that the subjects received drugs on eight separate days. In addition to the drugs, placebos were given on two separate days. A minimum of 48 hours elapsed between drug treatments. Control measurements were taken one day prior to the start of the experiment, and again at its completion. The experimental design was a modified Latin square similar to that employed earlier (3).

All drugs, including placebos, were administered orally in identical capsules. Subjects did not eat breakfast on mornings that drugs were administered. The “double-blind” technique was employed throughout. Ninety minutes after the drug was given the following behavioural measures were recorded:

1. A modified digit symbol test: This test is similar to that in the Wechsler-Bellevue test (8) of adult intelligence. In order to minimize learning, a different code was used each time the subject received the test. Score was the number of digits correctly completed in a 90-second period.

2. Pursuit rotor: A standard Gerbrands machine rotating at 30 r.p.m. was used. The subject was required to maintain contact between a stylus held in the hand and a small electrical contact on the rotating turntable. Subjects were given eight trials of 30 seconds each. The duration of contact was recorded for each trial. Score was the mean of the eight trials.

3. Tapping speed: Subjects were required to tap as quickly as possible with a stylus on a metal plate. Five trials of 10 seconds each were recorded. Score was the mean number of taps for the five trials.

4. Tachistoscopic recognition of numbers: A modification of the Dodge tachistoscope (manufactured by Gerbrands) was used. Subjects were presented with a series of numbers consisting of from one digit to six digits at exposure speeds from .01 second up to the exposure time necessary for the subject to get three consecutive numbers of six digits correct. Exposure was increased at step intervals of .02 second. The score was the total number of errors.

5. Reaction time: Simple visual reaction time was recorded. These results are reported elsewhere (9).
Chronic Study

A minimum of one week after the completion of the acute study, subjects were placed on a two-week regime of chlorpromazine, secoarbital, or a placebo. All subjects received two weeks of each treatment according to a latin square design. The first week on either drug subjects received 100 mg. at 8.00 a.m. and at 8.00 p.m. for a total daily dose of 200 mg. The second week on either drug subjects received 200 mg. at 8.00 a.m. and 8.00 p.m. for a total daily dose of 400 mg. Subjects were tested 90 minutes after the morning medication on the fifth day of each drug week. Breakfast was omitted on testing days. The same tests employed in the acute study were used in the chronic study.

Treatment of Data

An analysis of variance (2) was computed from the data for each test. Since the usual t-test does not take into account the number of comparisons that were made, the significance of differences between the effects of placebos and drugs was obtained by the Dunnett t-test (1). The test of significance of differences between the effects of various doses of the drugs was computed by means of the Scheffé test (6). These two tests adjust the P level according to the number of comparisons made; the greater the number of comparisons, the greater the difference needed for significance.

Tables I and II show the results of the summaries of the analyses of variance for the acute and chronic study, respectively. It can be seen that on both the acute and chronic studies there was a significant F ratio for drugs on all tests except the tachistoscopic recognition of numbers. A significant F ratio for individuals was found on all tests in the chronic study, and in all tests but pursuit rotor in the acute study.

<table>
<thead>
<tr>
<th>Source</th>
<th>df</th>
<th>M.Sq.</th>
<th>F</th>
<th>M.Sq.</th>
<th>F</th>
<th>M.Sq.</th>
<th>F</th>
<th>M.Sq.</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs (D)</td>
<td>4</td>
<td>187</td>
<td>6.45*</td>
<td>249</td>
<td>5.93*</td>
<td>194</td>
<td>1.76</td>
<td>104</td>
<td>9.45†</td>
</tr>
<tr>
<td>Individuals (I)</td>
<td>11</td>
<td>754</td>
<td>62.80*</td>
<td>1,618</td>
<td>52.20†</td>
<td>1,657</td>
<td>3.17†</td>
<td>91</td>
<td>1.62</td>
</tr>
<tr>
<td>D × I</td>
<td>44</td>
<td>29</td>
<td>2.42†</td>
<td>42</td>
<td>1.35</td>
<td>110</td>
<td>0.21</td>
<td>11</td>
<td>0.20</td>
</tr>
<tr>
<td>Order</td>
<td>1</td>
<td>39</td>
<td>3.25</td>
<td>320</td>
<td>10.32†</td>
<td>2,651</td>
<td>5.08*</td>
<td>200</td>
<td>3.57</td>
</tr>
<tr>
<td>Error</td>
<td>59</td>
<td>12</td>
<td>—</td>
<td>31</td>
<td>—</td>
<td>522</td>
<td>—</td>
<td>56</td>
<td>—</td>
</tr>
<tr>
<td>Total</td>
<td>119</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*P < .05.  †P < .01.

<table>
<thead>
<tr>
<th>Source</th>
<th>df</th>
<th>M.Sq.</th>
<th>F</th>
<th>M.Sq.</th>
<th>F</th>
<th>M.Sq.</th>
<th>F</th>
<th>M.Sq.</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs</td>
<td>5</td>
<td>106</td>
<td>6.62†</td>
<td>177</td>
<td>6.32†</td>
<td>86</td>
<td>1.41</td>
<td>84.2</td>
<td>10.94†</td>
</tr>
<tr>
<td>Individuals</td>
<td>10</td>
<td>615</td>
<td>38.44†</td>
<td>972</td>
<td>34.71†</td>
<td>570</td>
<td>9.34†</td>
<td>41.0</td>
<td>5.32†</td>
</tr>
<tr>
<td>D × I</td>
<td>50</td>
<td>16</td>
<td>—</td>
<td>28</td>
<td>—</td>
<td>61</td>
<td>—</td>
<td>7.7</td>
<td>—</td>
</tr>
<tr>
<td>Total</td>
<td>65*</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

* One subject did not complete the experiment so that computations are based on 11 subjects.  †P < .01.
Figures 1 to 4 show results on individual tests for acute and chronic administration of both drugs. In each case performance was plotted as a percentage of the mean of the two placebo administrations.

**Acute Study**

Neither 100 mg. of chlorpromazine nor 100 mg. of secobarbital significantly impaired performance on any of the four tests. Both 200 mg. of chlorpromazine and 200 mg. of secobarbital caused significant impairment in performance on all tests (P<.01 on tapping speed and pursuit rotor and P<.05 for chlorpromazine on the digit symbol test) except tachistoscopic recognition.

A comparison between each of the drugs at each of the two dose levels indicated that on the tapping speed test 200 mg. of secobarbital produced significantly more impairment than both 100 mg. of secobarbital and 100 mg. of chlorpromazine (P<.05). On the digit symbol test 200 mg. of secobarbital caused significantly more impairment than 100 mg. of secobarbital (P<.05) and 100 mg. of chlorpromazine (P<.01), and 200 mg. of chlorpromazine had significantly more effect than 100 mg. of chlorpromazine (P<.05). On the pursuit rotor test 200 mg. of chlorpromazine had significantly more effect than both 100 mg. of chlorpromazine and 100 mg. of secobarbital (P<.01). No other comparisons yielded statistically significant differences.
Fig. 2.—Comparison of acute and chronic administration of chlorpromazine and secobarbital plotted as a per cent. of the placebo score on the digit symbol test.

Fig. 3.—Comparison of acute and chronic administration of chlorpromazine and secobarbital plotted as a per cent. of the placebo score on pursuit rotor test.
1959] BY C. KORNETSKY, M. PETTIT, R. WYNNE AND E. V. EVARTS 195

**Chronic Study**

The results after chronic administration of the drugs showed that chlorpromazine, which had the most marked effects on performance in the acute study, caused no statistically significant impairment in performance of the tests after chronic administration. Two hundred mg. of secobarbital caused significant impairment in functioning ($P < .01$) on all tests except tachistoscopic recognition. On every test except tachistoscopic recognition, 200 mg. of secobarbital produced more impairment than both 100 and 200 mg. of chlorpromazine ($P < .01$). On the pursuit rotor, the effect of 200 mg. of secobarbital was significantly greater than 100 mg. of secobarbital ($P < .05$).

**Discussion**

Comparison of the results of this study with the previous study of Kornetsky and Humphries (2) indicates both similarities and differences between schizophrenic patients and normal subjects in their responses to single doses of chlorpromazine and secobarbital. Secobarbital seems to cause approximately as much impairment in functioning in schizophrenics as it does in normals; however, although 200 mg. of chlorpromazine significantly impaired performance of patients on all tests except tachistoscopic recognition of numbers, 100 mg. did not significantly affect performance of the schizophrenic patients on any of the tests. This was not true in the normal subjects. Normal subjects were significantly impaired by 100 mg. of chlorpromazine on tapping speed and on the pursuit rotor. In addition, 200 mg. of chlorpromazine produced less impairment in the schizophrenic patients than in the normal subjects on tachistoscopic
recognition of numbers (Fig. 5) and on the pursuit rotor (Fig. 6). On the
tachistoscopic test 200 mg. of chlorpromazine caused no statistically significant
impairment in schizophrenics, whereas it produced marked impairment in

Fig. 5.—The effects of acute administration of chlorpromazine and secobarbital on the
performance of schizophrenic and control subjects on the pursuit rotor test.

Fig. 6.—The effects of acute administration of chlorpromazine and secobarbital on the
performance of schizophrenic and control subjects on the tachistoscopic perception test.
normals. Two hundred mg. of chlorpromazine caused a lesser degree of impairment in schizophrenic than in normal subjects on the pursuit rotor test. On both these tests, the schizophrenic patients performed more poorly than did normal subjects after placebo administration, but better than normals after 200 mg. of chlorpromazine. Figures 7 and 8 compare the performance of patients and

Fig. 7.—The effects of acute administration of chlorpromazine and secobarbital on the performance of schizophrenic and control subjects on the digit symbol test.

Fig. 8.—The effects of acute administration of chlorpromazine and secobarbital on the performance of schizophrenic and control subjects on the tapping speed test.
normal subjects on the digit symbol test and the tapping speed test. On these tests, the differential effect between normal and schizophrenic subjects was not found.

Daily administration of chlorpromazine to schizophrenic patients produces different effects from acute administration of single doses. At the end of a period of seven days of twice daily administration of 100 mg. of chlorpromazine followed by five days of twice daily administration of 200 mg., tests (given 90 minutes after a 200 mg. dose of chlorpromazine) failed to reveal significant impairment. However, when secobarbital was administered according to the same schedule, a 200 mg. test dose still caused significant impairment in performance, i.e. there was no evidence of tolerance. Single acute doses of 100 mg. of chlorpromazine produced a slight but not statistically significant effect. This small mean effect was no longer apparent after chlorpromazine had been administered for five days at a dose rate of 100 mg. twice daily. This suggests that tolerance to these effects is readily achieved in schizophrenic patients.

The results of this experiment indicate that the differences between the effects of single acute doses of chlorpromazine in normals (Kornetsky and Humphries (3)) and the effects of chronic administration of this drug may be attributed to the differences between chronic and acute administration of the drug. Our failure to observe improvement in performance after chronic administration of chlorpromazine may have been the result of the criteria we employed in the selection of patients. Whereas we used subjects who were co-operative, other investigators who have observed improved test performance following chlorpromazine may have selected subjects who were more disturbed and who were functioning at a level of performance far below their potential prior to the start of drug administration.

SUMMARY AND CONCLUSIONS

Twelve male schizophrenic patients who had been hospitalized for one or more years were tested on four psychological tests after both single doses and chronic (11 days) oral administration of chlorpromazine and secobarbital. The effects of single doses of both drugs were compared to those effects found in normal subjects after single oral doses of the same drugs in a previous experiment.

The following conclusions were drawn from the data:
1. Single doses of 200 mg. of both drugs caused a significant deficit in test performance.
2. After 11 days of chronic administration (seven days of 100 mg. twice daily and four days of 200 mg. twice daily) a 200 mg. test dose of chlorpromazine no longer impaired functioning; a 200 mg. test dose of secobarbital, given after a similar schedule of secobarbital administration, still significantly reduced level of performance.
3. Single doses of 100 and 200 mg. chlorpromazine caused less impairment in schizophrenic patients than in normal subjects.
4. Secobarbital impairs performance of schizophrenic patients and normal subjects to the same extent.

REFERENCES