PSYCHOLOGICAL EFFECTS OF CENTRALLY ACTING DRUGS IN MAN

EFFECTS OF CHLORPROMAZINE AND SECOBARBITAL ON VISUAL AND MOTOR BEHAVIOUR

By

CONAN KORNETSKY, M.S., Ph.D.

and

OGRETTA HUMPHRIES, B.S.

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

In a previous study (Kornetsky, Humphries and Evarts, 1957) it was found that the impairment of a variety of psychological processes caused by 200 mg. of chlorpromazine was not significantly less than the impairment produced by 200 mg. of secobarbital. It was also shown that the effects of drugs on psychological performance in man are related not only to the specific pharmacological activity of the drug, but also to the specific reactivity of the subject. It appeared that there was something unique to the individual which accounted for a significant portion of the effect of a drug. The present study was designed to extend these observations by reducing the number of drugs tested (in the previous study four drugs were used) and increasing the number of times a subject received each drug. It was hoped that this would give a better estimate of the effect of a specific dose of a specific drug and thus decrease the error of measurement and increase the reliability of the correlation between drugs.

Methods

Twelve normal volunteers between the ages of eighteen and thirty, five males and seven females, served as subjects. All subjects received the following drugs at the dosages indicated:

1. Chlorpromazine hydrochloride	100 and 200 mg.
2. Secobarbital sodium	100 and 200 mg.

Each drug at each dose was given twice so that the subjects received drugs on a total of eight days. In addition to the drugs, placebos were given on two separate days. There was also one control day prior to the start of the experiment and another at the completion of the experiment. The experimental design employed is shown in Table I. There was a minimum of one day between drug treatments. All drugs, including placebos, were administered orally in identical capsules. Subjects did not eat breakfast on mornings that drugs were to be given. The "double-blind" technique was employed throughout.

TABLE I

Experimental Design

Subject	Day									
	1	2	3	4	5	6	7	8	9	10
A	C-1*	S-2	P	S-1	C-2	S-2	C-1	P	C-2	S-1
B	C-2	S-1	P	S-2	C-1	S-1	C-2	P	C-1	S-2
C	S-2	C-1	P	C-2	S-1	C-1	S-2	P	S-1	C-2
D	S-1	C-2	P	C-1	S-2	C-2	S-1	P	S-2	C-1
E	C-1	S-1	P	C-2	S-2	S-2	C-2	P	S-1	C-1
F	C-2	S-2	P	C-1	S-1	S-1	C-1	P	S-2	C-2
G	S-1	C-1	P	S-2	C-2	C-1	S-1	P	C-2	S-2
H	S-2	C-2	P	S-1	C-1	C-2	S-2	P	C-1	S-1
I	C-1	C-2	P	S-2	S-1	C-2	C-1	P	S-1	S-2
J	C-2	C-1	P	S-1	S-2	C-1	C-2	P	S-2	S-1
K	S-1	S-2	P	C-2	C-1	S-2	S-1	P	C-1	C-2
L	S-2	S-1	P	C-1	C-2	S-1	S-2	P	C-2	C-1

* C-1: Chlorpromazine, 100 mg.; C-2: Chlorpromazine, 200 mg.; S-1: Secobarbital, 100 mg.; S-2: Secobarbital, 200 mg.; P: Placebo.

Ninety minutes after the administration of the drug, the following behavioural measures were obtained:

1. *A Modified Digit Symbol Test:* This test is generally similar to that in the Wechsler-Bellevue test (Wechsler, 1944) of adult intelligence. In order to minimize learning a different code was used each time the subject received the test.

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 sixteen trials of thirty seconds each. Eight of the trials were done under a mild shock motivation. The shock intensity was 1·9 milliamperes. The time of contact was recorded for each trial and the means for both motivated and unmotivated conditions were recorded.

3. *Hand Steadiness:* Subjects were required to hold a stylus in holes of various diameters for 10 seconds each. There were five holes ($\frac{1}{2}$ inch, $\frac{5}{8}$ inch, $\frac{1}{4}$ inch, $\frac{3}{8}$ inch and $\frac{5}{16}$ inch in diameter) and subjects were given two trials on each hole, one motivated and one unmotivated. In the motivated trials subjects received a mild electric shock to the fingers of the left hand when the stylus made contact with the side of the hole. Score was the mean time in contact. The greater the score the poorer the performance.

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

5. *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 of ·01 second up to the exposure time necessary for the subject to get three consecutive numbers of six digits correct. Exposure was increased at steps of ·02 second at a time. The score was the total number of errors.

At the completion of these tests, which lasted approximately one hour, subjects were allowed to rest for five minutes in a supine position. At this time a nurse recorded blood pressure, pulse, respiration, and oral temperature. Starting four hours after the administration of the drug, for a total of 17 hours,

nurses recorded whether the subject was asleep. The score was the total number of hours asleep during the seventeen hour period.

Treatment of Data: An analysis of variance (Edwards, 1946) was computed from the data for each test. The significance of differences between the effects of the drugs and the effects of the placebos was obtained by means of the single-tailed Dunnett *t*-test (Dunnett, 1955). Since a previous experiment (Kornetsky *et al.*, 1957) had indicated that both chlorpromazine and secobarbital impair functioning, there was no expectation that these two drugs would improve functioning in the present experiment; thus a single-tailed test was justified. The test of significance of differences between the effects of drugs was computed by means of the Scheffé test (Scheffé, 1953). To test whether or not the subjects who were most affected by one drug were also most affected by the other drugs, the product moment correlation (Edwards, 1946, p. 79) was computed and then the control score level was partialed out by means of partial correlations (Edwards, 1946, p. 125).

Results

Psychological effects: In every case the analysis of variance F ratio was significant for subjects, tests and drugs. Table II shows the mean score for all

Table II

Mean Scores on All Tests for All Experimental Conditions

Test	Control	Placebo	Chlorpromazine		Secobarbital	
			100	200	100	200
Digit symbol (No. correct)	69·5	69·2	65·6	63·1*	68·0	58·5*
Hand steadiness (in seconds)	·38	·29	·55*	·93*	·29	·32
Tapping speed (No. of taps)	78·5	78·2	73·9*	70·2*	77·6	73·7*
Pursuit rotor (Time in contact in seconds)	24·47	24·60	19·60*	14·93*	24·26	22·00*
Tachistoscopic (No. of errors)	21·79	12·67	17·83	50·92*	14·88	16·29
Sleep time (Median hours)		1·0	4·5*	8·0*	0·5	2·0

* Significant difference from placebo ($p < ·05$).

subjects on each test for each drug and dose. The Dunnett *t*-test was used to test the significance of the differences between the scores on each drug and dose with the placebo score. Since there were no significant differences between motivated and unmotivated conditions for the Pursuit Rotor and the Hand Steadiness tests, the motivated and unmotivated conditions were combined for each test. Since a balanced design was employed, day 1 and day 2 on the same dosage of a given drug were combined in computing mean effects without biasing the results.

Two hundred mg. of chlorpromazine produced a significant impairment of performance on the tests of Digit Symbol, Hand Steadiness, Tapping Speed, Pursuit Rotor, and Tachistoscopic Threshold. One hundred mg. of chlorpromazine produced significant impairment of performance on the tests of Hand Steadiness, Tapping Speed, and Pursuit Rotor.

Two hundred mg. of secobarbital caused significant impairment of performance on the Digit Symbol, Tapping Speed, and Pursuit Rotor tests. One hundred mg. of secobarbital caused no significant impairment of performance on any of the tests.

A comparison between the effects of each of the drugs at each of the two doses was carried out by means of the Scheffé test. This comparison indicated that on the Digit Symbol test 200 mg. of secobarbital produced significantly greater impairment in performance ($p < \cdot 05$) than either 100 mg. of secobarbital or 100 or 200 mg. of chlorpromazine.

On the Hand Steadiness test 200 mg. of chlorpromazine caused significantly greater impairment ($p < \cdot 05$) than any of the other drugs. One hundred mg. of chlorpromazine produced significantly greater impairment ($p < \cdot 05$) than either 100 or 200 mg. of secobarbital.

On the Tapping Speed test 200 mg. of chlorpromazine caused greater impairment of performance than any of the other drugs ($p < \cdot 05$). There was no significant difference in the degree of impairment of performance after 200 mg. of secobarbital and 100 mg. of chlorpromazine. Both these drugs at 200 mg. and chlorpromazine at 100 mg. dosage, respectively, produced greater impairment than 100 mg. of secobarbital ($p < \cdot 05$).

On the Pursuit Rotor test, 200 mg. of chlorpromazine produced significantly greater impairment ($p < \cdot 05$) of performance than any of the other drugs. One hundred mg. of chlorpromazine caused significantly greater impairment of performance on this test ($p < \cdot 05$) than 200 and 100 mg. of secobarbital. Two hundred mg. of secobarbital caused significantly greater impairment ($p < \cdot 05$) than 100 mg. of secobarbital.

On the Tachistoscopic Threshold test 200 mg. of chlorpromazine caused significantly greater impairment ($p < \cdot 05$) of performance than any of the other drugs. On this test, no other drugs caused significant impairment.

Table II also shows the mean number of hours slept by each subject during the period of between 4 and 21 hours after the administration of the drug. Using the Mood Median test (Mood, 1950, p. 398) a χ^2 of 37·9 was obtained. Only 200 and 100 mg. of chlorpromazine produced significantly greater sleep time than the other drugs (including placebo).

In order to test the hypothesis that subjects who are most affected by one drug are also most affected by the other drugs, the Pearson Product Moment correlation was computed between the effects of each drug and the effects of all the other drugs. The original ability of the subjects was partialed out by means of partial correlations. This was done for each test used. Table III shows

TABLE III

Mean Partial Correlations of all Experimental Treatments for Each Test

	Tapping Speed	Hand Steadiness	Digit Symbol	Pursuit Rotor	Tachistoscopic Threshold
Mean ..	·516	·570	·512	·439	·120
Range ..	·237–·680	·286–·894	0·64–·848	−·015–·785	−·348–·663

the means of these partial correlations for each test. In all but one case these mean correlations were substantial (·44 to ·57). The exception was that computed from the tachistoscopic perception test (·12).

Physiological effects: Only temperature and pulse yielded a significant analysis of variance F ratio for drug treatments and in both cases 100 and 200

mg. of chlorpromazine produced a significant effect under the conditions of the experiment. Table IV shows the mean physiological values for each drug.

TABLE IV

Mean Changes in Systolic Blood Pressure, Respiratory Rate, Pulse and Oral Temperature

Sign	Chlorpromazine		Secobarbital		
	100 mg.	200 mg.	100 mg.	200 mg.	Placebo
Blood pressure[a]	111·42	112·00	107·62	107·50	109·42
Respiration[b] ..	17·25	18·00	18·17	18·92	18·33
Pulse[b]	73·17*	75·25*	65·67	67·00	65·75
Temperature[c] ..	36·24†	36·05†	36·48	36·49	36·63

* $P < ·05$ between score and placebo score.
† $P < ·01$ between score and placebo score.
[a] mm. of mercury.
[b] per minute.
[c] degrees centigrade.

COMMENT

The results of this experiment indicate that in most tasks involving motor co-ordination 100 mg. of chlorpromazine causes greater impairment of performance than 200 mg. of secobarbital. However, in a task that is related to intellectual function (Digit Symbol) 200 mg. of secobarbital produced significantly greater impairment than 200 mg. of chlorpromazine, although the latter did cause significantly more impairment than the placebo. Perception as measured by the tachistoscopic threshold was affected only by 200 mg. of chlorpromazine. In the previous study (Kornetsky, Humphries and Evarts, 1957) secobarbital appeared to have greater effects on intellectual function than chlorpromazine and about the same effects on a motor task (Pursuit Rotor). These differences were not statistically significant. In the present study, in which each dose of the drug was repeated, significant differences were found between the effects of chlorpromazine and secobarbital. Chlorpromazine caused greater impairment of performance than did secobarbital.

In order to determine if the differences in effects between chlorpromazine and secobarbital could have been caused by the shorter duration of action of secobarbital a brief additional experiment was performed. In this experiment eight subjects were tested seven times on Tapping Speed and the Digit-Symbol test in a 170-minute period immediately after receiving 200 mg. of secobarbital. Table V shows the times of testing and results of this experiment for both

TABLE V

Effects on Digit Symbol Test and Tapping Speed Test at Various Times after Secobarbital Administration

Time since drug administration (in minutes) ..	5–25	30–50	55–75	80–100	105–125	130–150	155–175
Digit symbol	94·1*	67·2	67·8	77·2	79·3	87·1	90·0
Tapping speed	94·0	78·2	78·8	83·3	85·7	87·5	90·0

* Per cent. of control values.

Tapping Speed and the Digit-Symbol test. As can be seen the maximum effect is reached between 55 and 75 minutes after the drug and is still quite marked up to 125 minutes. In the main experiment all testing was done between 90 and 120 minutes after the drug was administered so that it is unlikely that the differences found between secobarbital and chlorpromazine could be the result

of testing after the effects of secobarbital had worn off. Also, in the main experiment the Digit-Symbol test was administered immediately following the Tapping Speed test. The former takes 90 seconds to complete and the latter approximately five minutes.

The differences in effects between chlorpromazine and secobarbital can possibly be explained merely as a function of differences in dose. This explanation would be most parsimonious if chlorpromazine had a greater effect than secobarbital on all the various tests; however, the reversal of effects found on the Digit-Symbol test indicates that at the doses of the drugs used, secobarbital does have a greater effect on the Digit-Symbol test than chlorpromazine and a lesser effect on the motor tasks. Obviously, if the dose of secobarbital was increased it is very likely that the effects on these other tasks would be as great as the effects of chlorpromazine; however, this would also increase the difference in effect of the two drugs on the Digit-Symbol test.

At the present time it cannot be stated that the same results would be obtained if the drugs were administered chronically. There is, indeed, evidence that tolerance does develop to both chlorpromazine and secobarbital. Also, it cannot be categorically concluded that schizophrenic patients (as contrasted to normal controls) who receive acute dosages of chlorpromazine would be equally impaired. It has been reported (Kovitz, Carter and Addison, 1955) that there is an improvement in intellectual performance of schizophrenic patients after the administration of chlorpromazine. Shaten *et al.* (Shaten, Rockmore and Funk, 1956) compared the effects of chlorpromazine and amobarbital and found that chlorpromazine had no inhibitory effect or facilitated performance on a variety of motor tasks, while amobarbital either had no effect or a deleterious effect on the performance of the same tasks. Since these investigators gave small doses of amobarbital intravenously a comparison of the observed effects of amobarbital with the effects of chronic oral administration of chlorpromazine is difficult to interpret. Lehmann and Hanrahan (Lehmann and Hanrahan, 1954) tested schizophrenic patients on a variety of psychological tests after the administration of chlorpromazine. They found that tapping speed was impaired in 50 per cent. of the subjects. There was no observed impairment on the other tests which were administered.

The findings of facilitation in performance on some tests and very little or no impairment in functioning on others, after chlorpromazine administration in schizophrenics, are contrary to the results of the present study. This suggests either that chronic chlorpromazine administration produces different effects than acute administration or that normal subjects react differently from schizophrenics after chlorpromazine. Further experimentation is at present under way to elucidate this point.

The observations on duration of sleep between 4 and 21 hours following drug administration showed that chlorpromazine caused a significantly greater period of sleep than secobarbital. The duration of sleep following secobarbital did not differ significantly from that following the placebo. This indicates that within four hours of drug administration the hypnotic effects of secobarbital were not apparent under the conditions of this experiment.

The mean partial correlations between the various experimental treatments (drugs and placebos) support the hypothesis that certain factors intrinsic to the individual subjects make them more or less sensitive to drugs of this type. The nature of these factors has not been elucidated; however, there is some evidence (Kornetsky and Humphries, 1957) suggesting that personality plays a role in drug responsivity. This does not imply that there cannot be a subject

X drug interaction, for there obviously is such an interaction. However, there is still a significant tendency for some subjects to show a greater effect than others no matter what drug they are given.

Although the mean effect produced by placebos (compared to the control) was not significant, there was a relationship between placebo scores and drug scores. This suggests that those subjects who were most affected by the placebos were also most affected by the drugs. This agrees with previous studies (Lasagna *et al.*, 1954) which demonstrated that placebo responders also obtained the greatest relief from pain after analgesics.

Summary and Conclusions

Twelve normal volunteers were given 100 and 200 mg. of chlorpromazine and 100 and 200 mg. of secobarbital on separate days. All drugs were administered orally and the "double-blind" technique was employed throughout. Ninety minutes after the ingestion of the drug, subjects were tested on a variety of psychological tests, and 210 minutes after the drug, blood pressure, pulse, respiration and oral temperature were recorded.

The following conclusions were drawn from the data:

1. At doses of 100 and 200 mg. chlorpromazine has a greater effect on tests of motor co-ordination than 100 and 200 mg. of secobarbital, respectively.
2. Two hundred mg. of secobarbital has a greater effect on a test that is related to intellectual functioning than 200 mg. of chlorpromazine.
3. Four hours after oral ingestion of chlorpromazine and secobarbital, sleep time is significantly increased for both 100 and 200 mg. of chlorpromazine, but not for secobarbital.
4. This study supports a thesis of general drug sensitivity in human subjects. Subjects most affected by one drug are most affected by other drugs.

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