EFFECTS OF CHRONICALLY ADMINISTERED CHLORPROMAZINE ON MULTIPLE-SCHEDULE PERFORMANCE¹

MARCUS B. WALLER²

ROSCOE B. JACKSON MEMORIAL LABORATORY

The purpose of this research was to establish multiple schedules which would have the characteristics of stability of over-all rates from session to session, yet show definite signs of poor stimulus control; and also to analyze experimentally the effects of chronic doses of chlorpromazine on these behavioral base lines.

There is reason to believe that an unstable discrimination may be particularly sensitive to the effects of drugs. For example, Dews (1955) has shown that stable discriminations, controlled by simple stimuli showing high discriminability, are relatively unaffected by pentobarbital, methamphetamine, and scopolamine in several doses. However, a slightly less stable discrimination, controlled by complex stimuli of low discriminability, was grossly disrupted by pentobarbital and methamphetamine, but not scopolamine. Thus, the effect of drugs on behavior controlled by discriminative stimuli appears to be a function of the degree of stimulus control. Further, the degree of stimulus control can be manipulated by varying the discriminability of the stimuli.

Several considerations dictated that chlorpromazine be used in the present experiments. Dews (1958a) demonstrated that chlorpromazine and promazine had similar effects on mixed-schedule performance. At low dose levels, both drugs led to an increase in response output. This increase was a result of the subjects' responding for extended periods at the fixed-ratio rate after the schedule had changed to fixed interval. This effect was interpreted as a loss of stimulus control. Dews (1958b) has also suggested that chlorpromazine and other drugs may affect stimulus control when the behavior is controlled by external stimuli, *i.e.*, multiple schedules.

Because the major interest of the present experiments was the effects of the drug on discriminative control, specific dose-response functions were ignored. Instead, an effort was made to investigate the effects of chronic administrations of chlorpromazine. In order to maximize chronicity with a single drug administration each day, spansules (sustained release capsules) were used. The use of spansules further confuses the issue of specific dose levels. This was not considered critical, however, since relative dose levels were sufficient to demonstrate effects on stimulus control over some (admittedly indeterminate) dose range.

¹The research reported herein was supported by Grant MY-1775 from the National Institute of Mental Health of the USPHS. This paper was presented to the Eastern Psychological Association, Atlantic City, N. J., 1959.

²Now USPH Postdoctoral Fellow, Department of Pharmacology, Harvard Medical School.

METHOD

Subjects

The Ss were two purebred, male, beagle dogs (littermates) from the colony maintained by the Roscoe B. Jackson Memorial Laboratory.

Subjects were maintained on approximately 225 grams per day of Big Red dog chow,³ all of which was received in the experimental situation. Weekly supplements of Vitatone⁴ were also given to maintain good health. This regimen maintained the animals at approximately 80% of their free-feeding weights.

The reinforcement histories of the Ss were somewhat different. Subject A had been maintained on FI 3 for an extended period, whereas Subject B had been maintained on FR 120 for a similar period. Also, a variety of multiple schedules was run before arriving at the schedules which were used. To eliminate the effects of previous histories of reinforcement and find a stable base line, Ss were maintained on the final schedules for approximately 400 hours before the initial experimental session.

Apparatus

The apparatus consisted of a box enclosure 36 inches wide, 36 inches long, and 30 inches high, which had a grid floor and was ventilated by an exhaust fan. The operant maintained was one of nosing a specially constructed manipulandum (Waller, 1960). This manipulandum consists of a housing (made of sheet metal) which contains a bar that the animal raises with its nose to complete a circuit through a micro-switch. This device was mounted at the center of the rear wall of the enclosure approximately 17 inches above the grid floor.

The discriminative stimuli were three pilot lights, each 1 inch in diameter, mounted 15 inches above the grid floor on the same wall as the manipulandum. They were distinctive by virtue of their spatial location, one being on the extreme right, one on the extreme left, and the third directly beneath the manipulandum. The light on the extreme left was correlated with the interval component, and the light on the extreme right, with the fixed-ratio component. The S^A component was correlated with the center position. These stimuli were designed to present S with a difficult discrimination, comparable to that used by Dews (1955).

For reinforcement, Ss received pellets of Big Red dog chow, each weighing approximately 4 grams. The

³G.L.F. Cooperative Exchange, Inc., Canandaigua, N. Y.

⁴Fort Dodge Laboratories, Inc., Fort Dodge, Iowa.

reinforcements were delivered by a Gerbrands² universal feeder through a tube arrangement. All programming was done with a system of relays, counters, and timers.

Schedules

The multiple schedules used for the two Ss were similar but not identical. Subject A was maintained on mult FI 3 FR 50 S^A 25 minutes, whereas Subject B was on mult VI 3 FR 50 S^A 25. Thus, the schedules differed in the interval components. The sequence of components within a session was held constant: 5 intervals, S^A, 10 ratios, 10 intervals, 5 ratios, S^A, 5 ratios, 5 intervals, S^A, 10 ratios, 5 intervals.

Both Ss were run 7 days a week, for approximately 3.5-hour sessions. When heavily drugged, Ss frequently required more time. All sessions were terminated after either 55 reinforcements and/or 6 hours. Only on rare occasions at high dose levels would an animal fail to reach the reinforcement criterion.

Drug Manipulation

Eight dose levels of chlorpromazine^a in spansule form were used: 1, 2, 4, 8, 12, 16, 20, and 24 mg/kg. The doses were administered orally 2 hours before the start of a session. Three complete replications of drug dosage were run on each S. A replication consisted of two successive daily sessions run at zero dose level, followed by the eight daily sessions during which the animals were drugged. The replications differed in that in one the order of dosage was ascending, *i.e.*, 1, 2, 4, 8, 12, 16, 20, and 24 mg/kg; in another, descending, *i.e.*, 24, 20, 16, 12, 8, 4, 2, and 1; and in the third, starting in the middle (mixed), *i.e.*, 12, 16, 20, 24, 1, 2, 4, and 8. Exact doses of spansule material were obtained by first weighing the contents of 20 each of the standard capsules to determine the weight of spansule material needed to obtain a particular quantity of chlorpromazine. The contents of all capsules were then placed in a small pill bottle. After the weights of spansule material required for each dose level were calculated for each S, appropriate quantities of spansule material were reweighed from the bottle and placed into standard capsules. To insure a random sampling of the various pellets, the bottle containing the spansule material was shaken thoroughly before each sample was taken.

RESULTS

Figure 1 shows the general effects of chronically administered chlorpromazine on each component of the multiple schedules. In this figure, responses per minute is plotted against the amount of spansule material administered 2 hours before the session. The two Ss

are shown separately. Each point represents the mean of three observations except at 1 mg/kg for Subject B, when only two observations were available.

The mean response rates reported here were determined by a sampling and measuring procedure. From each daily session, 10 fixed ratios, 10 intervals, and usually 2 S^A periods were selected from the same portion of the record and measured as to time and number of responses. Occasionally, only a single S^A period was available for measure when an S was highly drugged and a session had to be terminated. The sections selected were chosen because they usually fell between 3.5 and 5.5 hours after drug administration. This delay appeared optimal in that drug effects were stable and maximal during this period. The specific sections selected were those in *italics* in the schedule specification listed above.

The data in Fig. 1 have a number of interesting features. First, the two Ss were consistent in their response to the drug. The broken line represents the performance of Subject A, the FI 3 FR 50 S^A 25 ani-

Fig. 1. Combined data from three replications of drug doses showing the individual subjects' performance on each component of the schedule.

mal; and the solid line represents the performance of Subject B, the VI 3 FR 50 S^A 25 animal. Second, at the zero dose level, the over-all rates on the three components of the multiple schedule were different, as expected. The fixed-ratio rates were approximately twice as great as the interval rates, and the S^A rates were very nearly zero. Concerning drug effects, four points are conspicuous. First, low doses of chlorpromazine led to increased rates in both interval components. An increase in rate is also observable in the fixed ratio at the low dose levels. Second, there was a consistent difference between the administration of 8 and 12 mg/kg. Although 8 mg/kg had no obvious depressing effects on any component, 12 mg/kg re-

²R. Gerbrands, 15 Ronald Road, Arlington, Massachusetts.

^aChlorpromazine in spansule form was generously supplied by Smith, Kline & French Laboratories, Philadelphia, Pennsylvania.

Fig. 2. Subject A, Replication II: Drug effects on the FR component of mult FI 3 FR 50 S⁴ 25.

Fig. 4. Subject A, Replication I: Drug effects on the FI component of mult FI 3 FR 50 S⁴ 25.

Fig. 3. Subject B, Replication II: Drug effects on the FR component of mult VI 3 FR 50 S⁴ 25.

Fig. 5. Subject B, Replication I: Drug effects on the VI component of mult VI 3 FR 50 S⁴ 25.

sulted in a depression of all reinforced components. Third, the rate in the S^A components was elevated by all except the lowest doses. Fourth, considerable behavior was still observable following 24 mg/kg of span-sule chlorpromazine.

Figures 2, 3, 4, 5, and 6 show the specific effects of chlorpromazine on each component following drug administration. The differences between the over-all rates in these figures and those in Fig. 1 occurred because the recorder ran during the magazine cycle. Figure 2 shows the fixed-ratio performance for Subject A, Replication II, in which the order of dosage was ascending from 1 to 24 mg/kg. Three changes are evident as a function of drug increase. The drug appears to have an effect at the lower doses which takes the form of slightly longer delays after reinforcement and breaks in the runs. The breaks are occasionally seen as "knees," but also appear much later in the runs. These are coupled with small increases in running rates. Other effects appear at 12 mg/kg and higher. Rate is depressed and "knees" become a frequent occurrence. A kind of scalloping effect occurs in several places, and intermediate rates become evident. A recovery to a somewhat normal performance takes place at 20 and 24 mg/kg. This recovery may be a function of drug tolerance, since the order was ascending.

Figure 3 shows segments of the fixed ratio for Subject B, Replication II, in which the order of dosage was descending. The effects at 20 and 24 mg/kg in this series tend to support the tolerance hypothesis. Here, the other effects are approximately the same as those in Fig. 2.

Figure 4 shows segments of FI performance taken from the cumulative records of Replication I after various drug administrations. The order of dose was mixed. The instability here has the characteristics of bursts of responses following a reinforcement, resulting in a knee-like effect; intermediate rates of responding without a true scallop effect; and breaks in the terminal rate. Also, after the higher doses, responding becomes very erratic, the record becomes grainy, and intermediate rates occur with a fairly high frequency. At doses above 8 mg/kg, short bursts of responses at a very high rate are particularly evident. These may be indicative of induction from the fixed-ratio component under high drug dosage. After low doses, the acceleration in rate is characterized by shorter delays after reinforcement, higher terminal rate, and less intermediate rate responding than that at the zero dose level. A few examples of breaks in terminal rate and some intermediate rates appear after low doses. The depression of responding after the 12 mg/kg dose is evident in the FI data. The control segment shown is typical of the FI behavior observed. The breaks in terminal rate, absence of scallops, and erratic responding after reinforcement are indicative of induction (Ferster & Skinner, 1957, p. 507).

Figure 5 shows samples of variable-interval responding after the various doses. One effect is an increase

Fig. 6. Subject A, Replication I: Drug effects on the S^A component of mult FI 3 FR 50 S^A 25.

in over-all rate after the lower doses. Also, as the dose increases up to 8 mg/kg, the record becomes much less grainy and the breaks in running rate appear less frequently. Furthermore, after 4 and 8 mg/kg, virtually no intermediate rates are observed. After the higher doses, grain returns to the record, and the animal frequently runs in a burst of responses at a very high rate. Furthermore, particularly after the highest doses, these bursts are interspersed with extended periods of no responding.

Figure 6 shows the S^A component of Subject A, Replication I, for the various doses. Virtually no nonresponding occurred during the S^A at doses below 8 mg/kg, at which point the animal emitted approximately 250 responses during the 25-minute period. At 12 mg/kg, approximately 300 responses were emitted at a fairly high rate. There was no responding at 16 mg/kg. Responding again occurred at 20 mg/kg, only to drop out again at 24 mg/kg. The S^A performance of Subject B was comparable.

DISCUSSION

Several results of this experiment deserve comment. First, response rates in all reinforced components increased following the administration of small amounts of span-sule chlorpromazine (Fig. 1). The increase was slight for ratio responding, but large for interval

responding. Two interpretations seem tenable: (1) The increase in rate is a simple drug effect; and (2) The increase is correlated with an independent drug effect. For the former interpretation to be correct, chlorpromazine must have a paradoxical effect when present in low concentrations. Dews (1958a) has shown such an effect on mixed-schedule base lines. The second interpretation requires that a mediating process be specified which is related to both the drug concentration and the increase in response output, though not necessarily by the same function. Dews (1958b) has suggested that chlorpromazine affects stimulus control. For a multiple schedule, greater induction would therefore be expected between components. Thus, the increase in rate at low drug concentration may be the result of the occurrence of ratio rates of response within the interval components.

This "loss of stimulus control" interpretation is also applicable to another result of the experiment, *i.e.*, the failure to decrease responding with massive amounts of chlorpromazine. Two other interpretations of this observation are also suggested. First, because of its gradual release and absorption, the spansule form of the drug requires a higher concentration to achieve the same effect as a rapidly absorbed administration of the drug. This interpretation is reasonable since most drugs show a different effective dose range depending upon the route of administration. The second alternative is that tolerance develops with repeated drug administration, particularly under the highly chronic conditions used.

Two further experiments were carried out to evaluate the alternative interpretations suggested above.

EXPERIMENT II

In order to assess the degree of induction between the components of the multiple schedules, Subject A was continued on mult FI 3 FR 50 S⁴ 25 until the base rate was stable on all components. The schedule was then changed to mult FI 3 FR ext S⁴ 25, and the FI component was observed at various points in the FR extinction process. Drug effects were then reassessed on this new base line.

Results

Figure 7 shows adjacent sections of the cumulative record for both the FI component (shown at the top) and the FR ext component (shown below). Each pair of sections represents a different session. The first three sections show the final performance on the FI and FR components while the FR was being reinforced. The next three pairs were taken from the first 3 days on mult FI 3 FR ext S⁴ 25. The FR ext was run as 1-hour sections within the multiple schedule. Daily sessions were approximately 7 hours, with 3 hours taken up by the FR ext. The change in FI performance as a function of FR extinction is obvious. The intermediate rates and breaks in terminal rate drop out completely. The delay after reinforcement

becomes much more pronounced as well as more consistent. The over-all rate decreases, whereas the running rates show little change. The last two paired sections shown were taken from the 15th and 25th sessions, respectively, and show the final form of response on both components.

These data indicate that a fairly high degree of induction was present during the initial observations of drug effects. However, they do not tell what part of the disruption observed under the various doses of chlorpromazine was due to induction.

To assess the extent to which induction might account for the drug effects in Experiment I, Subject A was run through the drug treatment procedure again after a stable performance had developed on mult FI 3 FR ext S⁴ 25. The eight doses of chlorpromazine used were the same as in the initial run, and the order of dose was ascending. Figure 8 shows samples of the cumulative record of the FI performance after each drug administration. According to this figure, the only appreciable change after doses of 1 and 2 mg/kg is a relatively small increase in terminal rate. The intermediate rates at the beginning of the scallops may be somewhat prolonged. Also, a large increase in over-all rate is obvious after 4 and 8 mg/kg, primarily because delays after reinforcement drop out. Whenever the delay is not completely omitted, it is appreciably shortened; and whenever scallops occur, the period of intermediate rate responding is somewhat accentuated. The break between 8 and 12 mg/kg is conspicuous. At the higher doses, the FI performance follows the increase in dosage, showing a rapid decline to a very low over-all rate. The last observation indicates the recovery from the effects of 24 mg/kg after 24 hours.

Discussion

A comparison of Fig. 8 with Fig. 4 shows the differential drug effects after FR extinction. The figures are similar in only one detail: the increase in rates after doses of 4 and 8 mg/kg. After these doses, chlorpromazine apparently leads to an increase in response rate which is independent of any induction from the FR component to the FI component. The maintenance of responding after the high doses is no longer present. Consequently, the responding observed after the high doses with the FR component intact is probably a function of induction, *i.e.*, loss of stimulus control.

The results of Experiment II clearly indicate that a high degree of induction from the fixed-ratio to the fixed-interval component was present during Experiment I. Whether chlorpromazine contributes to the loss of stimulus control and thereby increases induction cannot be determined from these experiments. However, the effects which can be attributed to induction at the higher doses of chlorpromazine suggest that this is so.

Drug tolerance cannot account for the differences observed between Fig. 4 and Fig. 8, because the chronic dosing procedure was used for both. However,

Fig. 7. Subject A: The effects of FR extinction on the FI performance on mult FI 3 FR ext S^A 25.

Fig. 8. Subject A: Drug effects on the FI component of mult FI 3 FR ext S^A 25.

the absolute effect of a particular dose may be a function of tolerance in both cases. The absolute effect may also be a function of a cumulative dose effect, since the drug was administered chronically and is known to have a persistent effect. However, on the basis of the results and also the final segment of Fig. 8, cumulative dose effect would seem to be less important.

EXPERIMENT III

To some extent, the drug effects in Experiments I and II are probably a function of drug tolerance. Thus, two questions must be considered. First, is there a systematic change in rates of response, in the direction of a return to base-line performance, as a function of prolonged chronic dosing with chlorpromazine? This can best be answered by repeatedly administering the same dose of the drug. The second question is: Will the tolerance (if there is any) which develops be effective following a change in dosage?

Procedure

To evaluate these questions, Subject A was continued on FI 3 (determined by dropping the S^A and FR extinction components of the previous multiple schedule) in 3-hour sessions until a reliable base line developed. This subject was then given a 30 mg/kg dose of chlorpromazine in spansule form immediately before a session began. Then, this subject was run 15 successive daily sessions before the drug tolerance observations began. For the drug tolerance observations, S was given a 16 mg/kg dose of chlorpromazine in spansule form 2 hours before the start of the session on 15 successive days. In the two daily sessions immediately following, S was again given the 30 mg/kg dose of spansule chlorpromazine as before. Drug was then withdrawn, and S continued on FI 3 to re-establish the base line.

Results

The results of this procedure are shown in Fig. 9, 10, and 11. Figure 9 shows the effects of chronic ad-

Fig. 9. Results of the drug tolerance procedure.

ministration of 16 mg/kg of spansule chlorpromazine over a 15-day period. The control value was derived from the three sessions immediately preceding the 15 drug days. The output ratio represents the performance during the last hour of each daily 3-hour session. This means that the figure shows drug effects during the fourth hour after drug administration, where the drug effects were maximal. The line superimposed on the points was fitted by eye and is intended merely to show the trend of the data. This figure clearly shows that drug tolerance develops over a 15-day period. The mean output ratio for the last 3 days is approximately 2.7 times the mean output ratio for the first 3 days. This is true in spite of the likelihood that the drug accumulates, so that the true dose level is somewhat greater on the last 3 days.

Cumulative dose effects make the interpretation of the data in Fig. 10 equivocal. The top line shows the effect of the 30 mg/kg dose of chlorpromazine before the tolerance procedure was carried out. The two curves below show the effects of the same drug administration on performance during the two sessions immediately after the tolerance procedure had been completed. Three features are of interest: (1) The time lag between drug administration and a gross depression in response rate is quite similar in the three observations; (2) The absolute rates of response after maximal depression are nearly the same in all three cases; and (3) The early portions of the curves show a higher rate for the pre-tolerance curve than for the two post-tolerance curves.

Fig. 10. Temporal effects of a 30 mg/kg dose of spansule chlorpromazine on FI 3 performance before and after establishing tolerance.

Discussion

Tolerance to chlorpromazine was shown to develop over a 15-day period when the drug was given once daily in spansule form. Because tolerance develops, the drug effects reported in Experiments I and II must be viewed accordingly. Probably, the drug effects observed in these experiments are less than those which would have resulted from a less chronic drugging procedure.

The question of how varying the dose level daily relates to the development of tolerance remains unanswered. The data were equivocal. If the two records after drug tolerance had shown a definite decrease in the depression with a 30 mg/kg drug administration, an explicit argument might be made. Since they did not, the only possible argument is that because of cumulative drug effects, the rates after the tolerance procedure would have been lower had tolerance not developed. A more explicit demonstration is demanded.

Withdrawal Effect

Quite independent of the experimental analysis of chlorpromazine effects on multiple-schedule performance was the observation of what appeared to be a

Fig. 11. Cumulative records showing the second hour of sessions following withdrawal of chlorpromazine (spansule). Schedule: FI 3.

drug withdrawal effect following the development of tolerance. Figure 11 shows the cumulative record of the second hour of the 1st, 2nd, 3rd and 8th, 9th, and 10th daily sessions following the post-tolerance II session in Fig. 10. The first record looks relatively normal, although the onset of responding after reinforcement tends to be abrupt. However, the second record shows an even greater tendency in this direction, with very few of the intervals showing a normal scallop. On several occasions, only a single response was made in an interval. The third record is an extreme example of the second-day performance. Days 4 and 5 have

been deleted. Following a week end on which the animal was not run, Record 8 was obtained. Although it still is very disrupted, this record shows some signs of returning to base line. Records 9 and 10 show a continued change toward an almost-normal performance.

The delay of onset, the performance (showing periodic suppression of responding interspersed with an unusual high-rate response pattern), and the gradual return to a normal performance suggest that something akin to a withdrawal syndrome may have been operating. The reproducibility and investigation of this phenomenon await further research.

SUMMARY

An effort was made to analyze experimentally the effects of chronic administrations of chlorpromazine on multiple-schedule performance with particular emphasis on the effects on stimulus control. This resulted in a series of experiments, each designed to clarify the issue in question. As a result, these conclusions can be drawn:

(1) Low doses of chlorpromazine lead to an increase in rates of response in all components of the multiple schedule used. This is partially a result of an increase in running rates, but it is also related to a disruption of characteristic fixed-interval and S^A performance. Subjects tended to respond more in the typical delay after reinforcement on the fixed interval and to show greatly increased responding to the S^A 's.

(2) At higher dose levels, rates were not depressed to the extent one would expect in the interval components. Analysis indicated this was due to induction from the fixed-ratio component of the schedule. When the FR component was extinguished, the expected depression occurred. The extinction of the FR component also indicated that a high degree of induction was present when the FR was intact.

(3) Since the likelihood of drug tolerance exists in any chronic dosing procedure, an attempt was made to establish the contribution of tolerance to the effects observed. Because of equivocal results, this was not possible. However, it was established that tolerance can occur with chronic administration of chlorpromazine. Thus, the values of the drug effects are relative, not absolute.

(4) Some indication of a withdrawal effect was observed.

REFERENCES

- Dews, Peter B. Studies on Behavior. II. The effects of pentobarbital, methamphetamine, and scopolamine on performances in pigeons involving discriminations. *J. Pharmacol. & exp. Therap.*, 1955, **115**, 380-389.
- Dews, Peter B. The effects of chlorpromazine and promazine on performance on a mixed schedule of reinforcement. *J. exp. Anal. Behav.*, 1958, **1**, 73-82. (a)

- Dews, Peter B. Analysis of effects of psychopharmacological agents in behavioral terms. *Fed. Proc.*, 1958, **17**, 1024-1030. (b)
- Ferster, C. B., and Skinner, B. F. *Schedules of reinforcement*. New York: Appleton-Century-Crofts, 1957.
- Waller, M. B. A manipulandum for use with dogs. *J. exp. Anal. Behav.*, 1960, **3**, 311-312.
- Received February 28, 1961.