Pharmacology Biochemistry & Behavior, Vol. 17, pp. 353–357, 1982. Printed in the U.S.A.

Phencyclidine in Combination with Pentobarbital: Supra-Additive Effects on Complex Operant Behavior in Pigeons[1]

DONALD M. THOMPSON AND JOSEPH M. MOERSCHBAECHER

Georgetown University Schools of Medicine and Dentistry, Washington, DC 20007

Received 5 February 1982

THOMPSON, D. M. AND J. M. MOERSCHBAECHER. *Phencyclidine in combination with pentobarbital: Supra-additive effects on complex operant behavior in pigeons.* PHARMAC. BIOCHEM. BEHAV. 17(2) 353–357, 1982.—Pigeons acquired a different four-response chain each session by responding sequentially on three keys in the presence of four colors. The response chain was maintained by food presentation under a fixed-ratio schedule. Errors produced a brief timeout but did not reset the chain. When phencyclidine was administered alone, the overall response rate decreased and the percent errors increased with increasing doses. Similar effects were found with a high dose of pentobarbital alone. When phencyclidine was administered in combination with pentobarbital, the phencyclidine dose-effect curves for rate and accuracy shifted to the left as the dose of pentobarbital was increased. Combinations of phencyclidine with a high dose of pentobarbital produced supra-additive effects; i.e., the effects on rate and accuracy were greater than expected from simple addition of the effects of each drug given alone. These results extend the generality of previous findings in patas monkeys in a similar repeated-acquisition task.

Repeated acquisition Response chains Fixed-ratio schedule Drug interaction Phencyclidine Pentobarbital Key peck Pigeons

IN a review of the behavioral pharmacology of phencyclidine, Balster and Chait [1] pointed out that the interactions between phencyclidine and other drugs of abuse was an area needing further study. In one such experiment, Chait and Balster [4] investigated the effects of phencyclidine in combination with pentobarbital in squirrel monkeys responding under a variable-interval schedule of food presentation. It was found that most dose combinations of phencyclidine and pentobarbital produced ". . .less disruption of responding than expected from simple addition of the effects of each drug given alone" ([4] p. 201). In fact, one could argue from the data that the two drugs generally interacted antagonistically (cf. [5]). Chait and Balster [4] suggested that such an interaction may be species-dependent since other research [2,5], using an observational rating scale of "behavioral depression," indicated that phencyclidine-pentobarbital combinations produced supra-additive effects in rhesus monkeys, but not in squirrel monkeys. (The effects are described as supra-additive rather than synergistic because the former term has a more precise quantitative meaning [7].) A supra-additive interaction between phencyclidine and pentobarbital was also found in a recent study with rhesus monkeys responding under a fixed-interval schedule of food presentation [14].

In a recent study with patas monkeys, Thompson and Moerschbaecher [13] examined the effects of phencyclidine in combination with pentobarbital on behavior in a repeated-acquisition task. The monkeys acquired a different four-response chain each session by responding sequentially on three keys in the presence of four geometric forms. The response chain was maintained by food presentation under a fixed-ratio (FR) schedule. Errors produced a brief timeout but did not reset the chain. When phencyclidine and pentobarbital were administered alone, the higher doses of each drug decreased the overall response rate and increased the percent errors. When phencyclidine was administered in combination with pentobarbital, the phencyclidine dose-effect curves for both rate and accuracy generally shifted progressively to the left as the dose of pentobarbital was increased. In two of three monkeys, combinations of phencyclidine with a high dose of pentobarbital consistently produced greater rate-decreasing and error-increasing effects than expected from simple addition of the effects of each drug given alone. In other words, the phencyclidine-pentobarbital combinations produced supra-additive effects.

Given the apparent species differences among primates in the behavioral effects of phencyclidine-pentobarbital combinations [2, 4, 5, 13, 14], an investigation of the effects of such

[1]This research was supported by U. S. Public Health Service Grants DA 01528 and DA 02679. Reprints may be obtained from D. M. Thompson, Department of Pharmacology, Georgetown University Schools of Medicine and Dentistry, Washington, DC 20007.

combinations on operant behavior in a non-primate species would be of interest. The purpose of the present study was to examine the effects of phencyclidine-pentobarbital combinations on the responding of pigeons in a repeated-acquisition task similar to the one used with patas monkeys [13].

METHOD

Subjects

Two adult male White Carneaux pigeons (P-7865 and P-2252) were maintained at approximately 80% of their free-feeding body weights (i.e., at 450 g) by food presented during the sessions and by postsession supplemental feeding. Water and grit were always available in the home cages. Both subjects had an extensive history of repeated acquisition of four-response chains under FR schedules; both had also served in a previous drug study [12].

Apparatus

The experimental space was a standard three-key pigeon chamber (BRS/LVE model SEC-002). Each translucent response key required a minimum force of 0.18 N for activation. Each key could be transilluminated by three Sylvania 24ESB indicator lamps, one with a red plastic end cap, one with a green cap, and the third with no cap. To provide a fourth color, "yellow" (actually yellow-orange) was produced by the red and green lights being on simultaneously. The control equipment consisted of timers, steppers, and associated relay circuitry; recording was by counters, running-time meters, and a cumulative recorder. White noise was continuously present in the chamber to mask extraneous sounds.

Procedure

Baseline. All three response keys were illuminated at the same time by one of four colors, either yellow, green, red, or white. The pigeon's task was to acquire a four-response chain by pecking the correct key in the presence of each color, e.g., keys yellow—Left correct; keys green—Right correct; keys red—Center correct; keys white—Right correct; reinforcement. The same chain (in this case, Left-Right-Center-Right or LRCR) was repeated throughout a given session. The four-response chain was maintained by food presentation under an FR 5 schedule; i.e., every fifth completion of the chain was followed by 3-sec (P-2252) or 5-sec (P-7865) access to mixed grain. Presentation of the grain magazine was accompanied by the offset of the keylights and the onset of the magazine light. All other completions of the four-response chain produced a 0.5-sec flash of the magazine light, which was accompanied by the offset of the keylights. When the pigeon pecked an incorrect key (e.g., the left or right key when the center key was correct), the error was followed by a 5-sec timeout. During the timeout, the keys were dark and responses were ineffective. An error did not reset the chain; i.e., the keylights after the timeout were the same color as before the timeout. Each session was terminated after 40 food reinforcements or 2 hr, whichever occurred first. A "blackout" (all lights off) of variable duration preceded and followed each session. Sessions were conducted daily, Monday through Friday.

To establish a steady state of repeated acquisition, the four-response chain was changed from session to session. The chains were carefully selected to be equivalent in several ways and there were restrictions on their ordering across sessions [11]. An example of a typical set of six chains is as follows: LRCR, CLRL, LRLC, RCRL, CLCR, RCLC; the order of the associated colors was always the same: yellow, green, red, white (food on the FR 5 schedule).

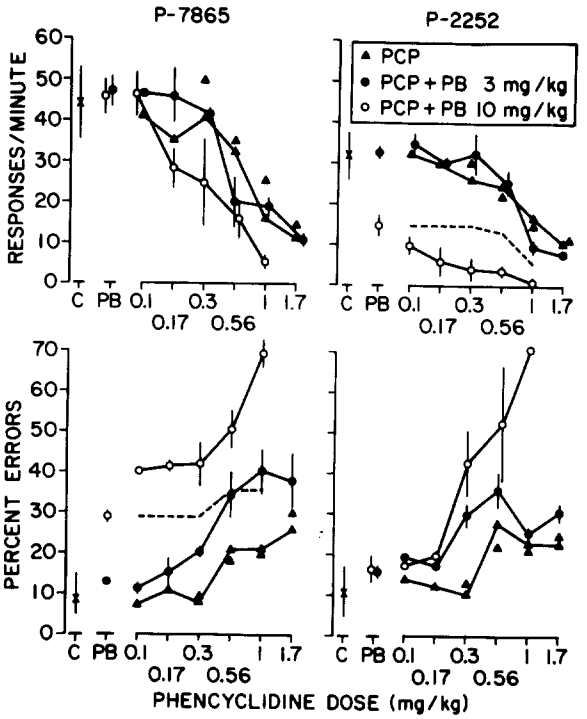

FIG. 1. Effects of phencyclidine (PCP) and pentobarbital (PB), alone and in combination, on the overall response rate and percent errors for each subject. The points and vertical lines at C indicate the mean and range for 18 to 20 control (saline) sessions. The points and vertical lines at PB indicate the mean and range for two determinations at each dose of pentobarbital alone, with the symbols the same as those for phencyclidine + pentobarbital. The points with vertical lines in the dose-effect curves indicate the mean and range for two determinations; the points without vertical lines indicate either a single determination or, occasionally, an instance in which the range is encompassed by the point. The unconnected triangles show a redetermination of the dose-effect data for phencyclidine alone after phencyclidine was tested in combination with pentobarbital. The dashed lines show the predicted outcome of combining phencyclidine with pentobarbital if the effects of phencyclidine alone (connected triangles) and the effects of pentobarbital alone (10 mg/kg) were additive.

The data for each session were analyzed in terms of (a) the overall response rate (total responses/min, excluding timeouts) and (b) the overall accuracy or percent errors [(errors/total responses) × 100]. In addition to these measures based on session totals, within-session changes in responding were monitored by a cumulative recorder. For example, acquisition of a response chain was indicated by within-session error reduction, i.e., a decrease in the frequency of errors (per reinforcement) as the session progressed.

Drug Testing. Before the drug testing began, the behavior under the baseline schedule was stabilized. The behavior was considered stable when the response rate and the percent er-

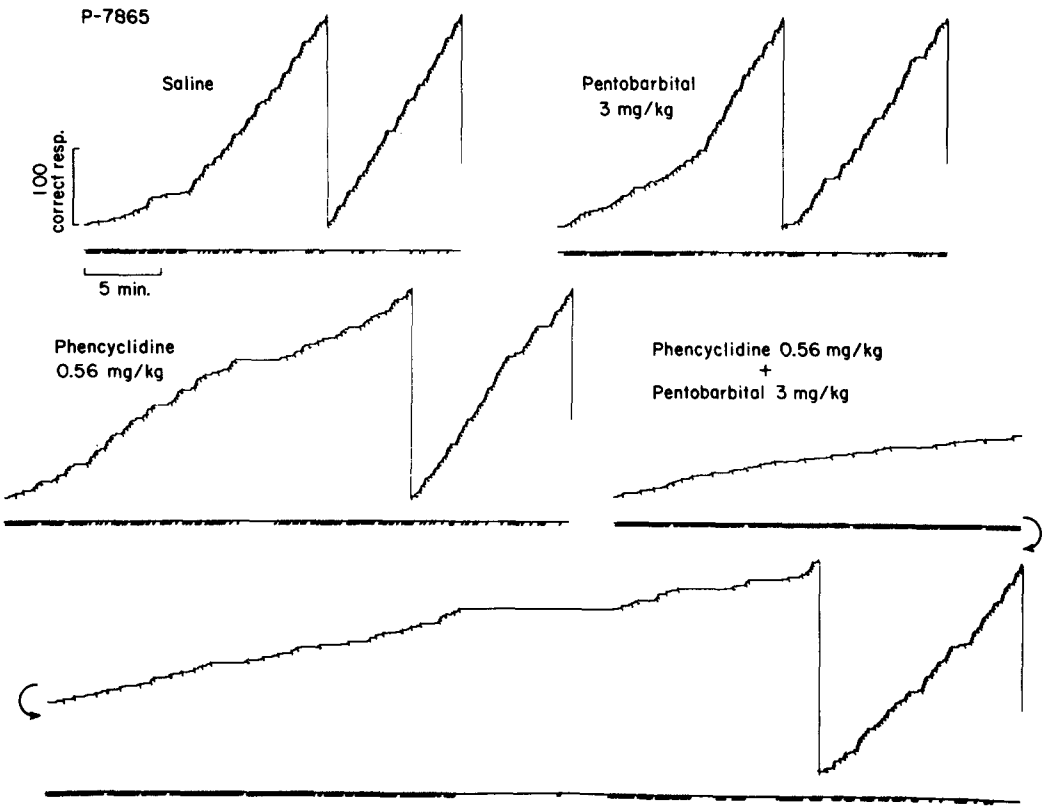

FIG. 2. Cumulative records for P-7865 showing the pattern of responding during a representative control session (saline) and during sessions preceded by injections of pentobarbital (3 mg/kg) and phencyclidine (0.56 mg/kg), alone and in combination. The first two excursions of the response pen in each session are shown. The response pen stepped upward with each correct response and was deflected downward each time the four-response chain was completed. Errors are indicated by the event pen (below each record), which was held down during each timeout.

rors no longer showed systematic change from session to session. After baseline stabilization (15–20 sessions), dose-effect data were obtained for phencyclidine hydrochloride. The drug was dissolved in saline (0.9%) and injected into the breast muscle 5 min presession. The doses of phencyclidine were tested in a mixed order. Next, 3 mg/kg of pentobarbital sodium, dissolved in saline, was administered alone (IM, 5 min presession). Varying doses of phencyclidine (in a mixed order) were then administered in combination with the 3 mg/kg dose of pentobarbital; two determinations were made for each combination. Both drugs were injected IM (one on the right side, the other on the left) 5 min presession. The 3 mg/kg dose of pentobarbital was then administered alone again. Next, using the same testing procedure, a higher dose of pentobarbital, 10 mg/kg, was administered alone and in combination with varying doses of phencyclidine. Finally, the dose-effect data for phencyclidine alone were redetermined.

Throughout testing, drug sessions were generally conducted on Tuesdays and Fridays, with control sessions (saline alone injected IM, 5 min presession) occurring on Thursdays, and baseline sessions (no injections) on Mondays and Wednesdays. Approximately one week of baseline sessions intervened between the end of a series of injections with one drug or drug combination and the start of a series with another. The volume of each injection was 0.1 ml/100 g body weight. All doses are expressed in terms of the salt of each drug.

RESULTS

Figure 1 shows the effects of phencyclidine and pentobarbital, alone and in combination, on the overall response rate and percent errors for each subject. When phencyclidine was administered alone (connected triangles), the response rate decreased and the percent errors increased with increasing doses. Note that the maximum error-increasing effect of phencyclidine occurred at different doses in the two subjects (1.7 mg/kg in P-7865 and 0.56 mg/kg in P-2252). When 3 mg/kg of pentobarbital, which had no effect when given alone, was administered in combination with phencyclidine, the dose-effect curves for percent errors were shifted to the left relative to those for phencyclidine alone. A similar shift in the dose-effect curves for response rate was much less evident, although there were reliable instances where this combination produced greater rate-decreasing effects than those produced by phencyclidine alone (i.e., P-7865 at 0.56 mg/kg and P-2252 at 1 and 1.7 mg/kg). The administration of

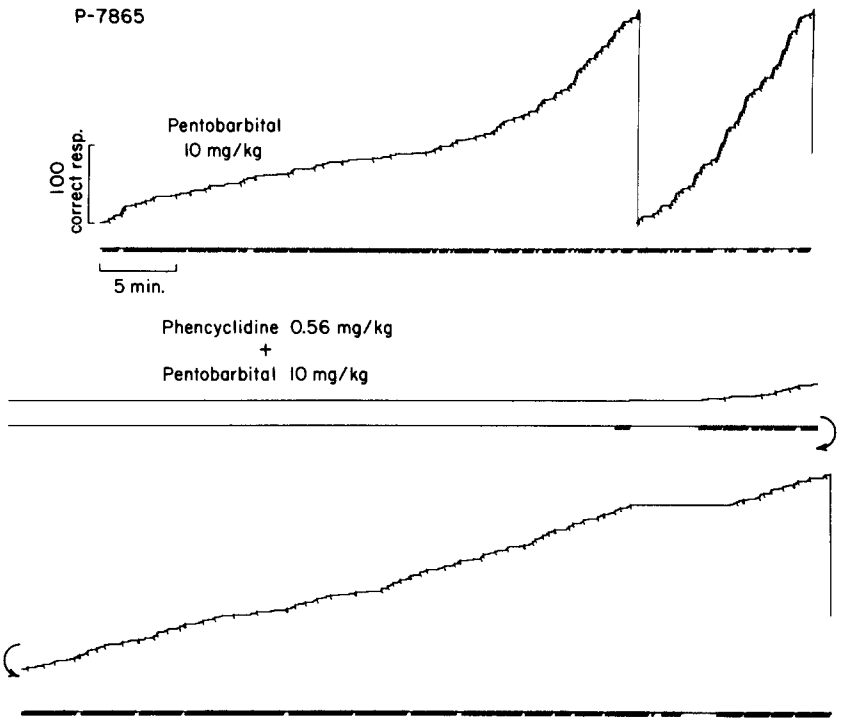

FIG. 3. Cumulative records for P-7865 showing the pattern of responding during two high-dose pentobarbital sessions: 10 mg/kg of pentobarbital alone and 0.56 mg/kg of phencyclidine in combination with 10 mg/kg of pentobarbital. The recording details are the same as in Fig. 2, except that only the first excursion of the response pen in the phencyclidine + pentobarbital session is shown.

10 mg/kg of pentobarbital alone decreased the response rate in P-2252 and increased the percent errors in P-7865. Despite these individual differences, this dose of pentobarbital in combination with phencyclidine shifted the dose-effect curves for both rate and accuracy further to the left than did the 3 mg/kg dose of pentobarbital in both subjects. In general, the effects of phencyclidine alone were replicated after the phencyclidine-pentobarbital combinations were tested (see the unconnected triangles).

The dashed lines in Fig. 1 show the predicted outcome of combining phencyclidine with pentobarbital if the effects of phencyclidine alone (connected triangles) and the effects of pentobarbital alone (10 mg/kg) were additive. (Dashed lines are not shown for response rate in P-7865 and percent errors in P-2252 since 10 mg/kg of pentobarbital alone had no effect in these cases; the predicted outcome here is simply the dose-effect curve for phencyclidine alone.) When administered alone, each drug was considered to have an effect on response rate or percent errors to the extent that the data points fell outside of the control range [13]. Accordingly, the rate-decreasing effect of phencyclidine alone was calculated by subtracting the overall response rate at a given dose of phencyclidine from the minimum control rate, yielding a difference score. If the response rate at a given dose of phencyclidine fell within the control range, the dose was considered to have no effect, and the difference score was assigned a value of 0. The same type of calculation was made for pentobarbital alone, and the sum of the two difference scores defined the additive effect on response rate (cf. [4]). The additive effect on percent errors was determined in the same way, except that the error-increasing effect of each drug alone was calculated by subtracting the maximum control value for percent errors from the percent errors at a given dose. As can be seen, when phencyclidine and pentobarbital (10 mg/kg) were administered in combination, the effects on rate and accuracy were greater than expected from simple addition of the effects of each drug given alone; i.e., the phencyclidine-pentobarbital combination produced supra-additive effects.

Figure 2 shows the pattern of responding during a representative saline session (one that approximated the mean for both overall response rate and overall accuracy) and during several drug sessions for P-7865. As can be seen in the saline record, errors decreased in frequency as the session progressed; i.e., acquisition occurred. After the first 7 min of this session, there were frequent runs of correct responses emitted at a high rate and relatively few errors were made. The runs of correct responses were often preceded by brief pauses. When 3 mg/kg of pentobarbital was administered alone, the pattern of responding was essentially the same as that seen in the saline sessions. This was not the case, however, when 0.56 mg/kg of phencyclidine was administered alone. During the first excursion of the response pen in this drug session, errors occurred at a higher frequency than during the saline sessions and there was increased pausing. Both effects were much more pronounced, however, when 0.56

mg/kg of phencyclidine was administered in combination with 3 mg/kg of pentobarbital, although within-session error reduction (acquisition) still occurred.

Figure 3 shows the within-session effects of 10 mg/kg of pentobarbital alone and in combination with 0.56 mg/kg of phencyclidine on the responding of P-7865. When 10 mg/kg of pentobarbital was administered alone, the frequency of errors was substantially increased in comparison to control (Fig. 2, top), but there was no increased pausing. In contrast, when this dose of pentobarbital was administered in combination with 0.56 mg/kg of phencyclidine, there was a long initial pause. When the subject began responding, errors occurred even more frequently than with 10 mg/kg of pentobarbital alone, and within-session error reduction was not evident. In general, the within-session effects of phencyclidine in combination with pentobarbital in P-7865 (Figs. 2 and 3) were replicated with the other subject, although the particular doses and the magnitude of the effects varied.

DISCUSSION

In the present study, the administration of phencyclidine alone produced a dose-related decrease in the overall response rate of pigeons in a repeated-acquisition task, where sequential responding on three keys was maintained under an FR schedule. This rate-decreasing effect was accompanied by an increase in percent errors. When pentobarbital was administered alone, the 10 mg/kg dose decreased the overall response rate in one subject and increased the percent errors in the other subject. Had higher doses of pentobarbital been tested (e.g., 17 mg/kg), it is likely that both effects would have been obtained in each subject [12]. The present results are generally consistent with previous research showing that phencyclidine and pentobarbital, when administered alone, produce similar dose-related disruptive effects on complex operant behavior. For example, Brown and Bass [3] found that both drugs disrupted the performance of rhesus monkeys in an oddity-discrimination task; each drug decreased the rate of correct responding in a dose-dependent manner and, at higher doses, increased errors. More recently, McMillan [9] reported that both phencyclidine and pentobarbital disrupted the performance of pigeons in a delayed matching-to-sample task; the higher doses of each drug decreased matching accuracy. Finally, in research more closely related to the present experiment, it was found that both phencyclidine and pentobarbital disrupted the behavior of patas monkeys in a repeated-acquisition task involving either conditional discriminations [10] or four-response chains [13]; in both cases, the higher doses of each drug decreased the overall response rate and increased the percent errors.

When phencyclidine was administered in combination with pentobarbital, the results obtained in the present study with pigeons were essentially the same as those previously found with patas monkeys in a similar repeated-acquisition task [13]. In both studies, (1) the phencyclidine dose-effect curves for rate and accuracy shifted to the left as the dose of pentobarbital was increased, and (2) combinations of phencyclidine with a high dose of pentobarbital produced greater rate-decreasing and error-increasing effects than expected from simple addition of the effects of each drug given alone. The generality of the findings in patas monkeys is therefore extended by the present research with pigeons.

The shift in the dose-effect curves in Fig. 1 cannot be attributed to the development of "supersensitivity" to phencyclidine (i.e., an increased sensitivity due to repeated drug administration) since the effects of phencyclidine alone were replicated after the phencyclidine-pentobarbital combinations were tested. Probably the most reasonable interpretation of the shift in the phencyclidine dose-effect curves is that pentobarbital "potentiated" the effects of phencyclidine (cf. [8]). This interpretation is supported by the present finding that phencyclidine and pentobarbital in combination produced supra-additive effects.

In summary, on the basis of the present study and previous research, it appears that phencyclidine-pentobarbital combinations produce supra-additive effects on operant behavior in pigeons, patas monkeys [13], and rhesus monkeys [14], but not in squirrel monkeys [4]. This conclusion, however, can only be tentative. As Dews ([6] p. 181) has pointed out, one of the criteria for species differences in drug effects on behavior is that "the species differ in how comparable patterns of behavior are modified by the drug." Such comparability has generally not been the case in studies of the effects of phencyclidine-pentobarbital combinations on operant behavior.

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