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

DONALD M. THOMPSON AND JOSEPH M. MOERSCHBAECHER

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

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THOMPSON, D. M. AND J. M. MOERSCHBAECHER. *Phencyclidine in combination with pentobarbital: Supra-additive effects on complex operant behavior in patas monkeys.* PHARMAC. BIOCHEM. BEHAV. **16**(1) 159–165, 1982.—In one component of a multiple schedule, patas monkeys acquired a different four-response chain each session by responding sequentially on three keys in the presence of four geometric forms (learning). In the other component, the four-response chain was the same each session (performance). The response chain in each component was maintained by food presentation under a fixed-ratio schedule. Errors produced a brief timeout but did not reset the chain. When administered alone, phencyclidine and pentobarbital, at the higher doses, generally decreased the overall response rate and increased the percent errors in both components. The performance component tended to be less sensitive than the learning component to the drug effects. 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 on responding under the multiple schedule.

Repeated acquisition Response chains Multiple schedule Drug interaction Phencyclidine Pentobarbital Key press Monkeys

WHEN administered alone, phencyclidine and pentobarbital have been reported to have similar effects on complex operant behavior. For example, Brown and Bass [2] 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 [6] 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.

In a study more closely related to the present experiment, Moerschbaecher and Thompson [7] compared the effects of phencyclidine and pentobarbital on the acquisition and performance of conditional discriminations in patas monkeys. In each of two components of a multiple schedule, the monkeys were required to respond on a right or left lever depending upon the stimulus combination (a color and a geometric form) presented. Reinforcement of a response in the presence of one stimulus (the form) was conditional upon the other stimulus (the color). The completion of a two-member chain of discriminations produced a food pellet; errors produced a brief timeout. One component of the multiple schedule was a repeated-acquisition task where the discriminative stimuli for left- and right-lever responses changed each session (learning). In the other component, the discriminative stimuli were the same each session (performance). Phencyclidine and pentobarbital each produced dose-related decreases in the overall rate of responding in both components of the multiple schedule. At high doses each drug increased the percent errors in each component. At lower doses, however, both drugs produced selective effects on accuracy. Errors were increased in the learning component at lower doses than those required to disrupt the discrimination in the performance component.

Although the foregoing studies have shown that phencyclidine and pentobarbital have similar effects on complex operant behavior, it does not necessarily follow that if the two drugs were administered in combination, their effects would be either additive or supra-additive. Instead, one might obtain the type of drug interaction reported by Chait and Balster [3]. In that study, the responding of squirrel monkeys was maintained under a variable-interval schedule of food presentation, and 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" ([3] p. 201). In fact, one could argue from the data that the two drugs generally in-

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teracted antagonistically (cf. [4]). Whether this finding could be extended to more complex behavior in a different primate species was a question that led to the present experiment. The purpose of the present experiment was to examine the effects of combined administration of phencyclidine and pentobarbital on the acquisition and performance of response chains in patas monkeys.

METHOD

Subjects

Three adult female patas monkeys served. Each subject had a long history of responding under the multiple-schedule baseline used in the present research (more than 1000 sessions), during which time a variety of drugs were tested, including *d*-amphetamine and cocaine [9] as well as phencyclidine and pentobarbital (administered separately). The testing of the latter two drugs was completed approximately four months prior to the start of the present study. The subjects were maintained at about 90% of their free-feeding weights (range 5.9 to 6.8 kg) on a diet consisting of Noyes banana-flavored food pellets, Purina Monkey Chow, fruit, and vitamins. The pellets were either earned during the experimental session or, when necessary, provided after the session. Monkey Chow, fruit, and vitamins were given to each subject after the daily session. Water was continuously available.

Apparatus

Each subject was housed in a primate cage (Research Equipment Co., model LC-1001) measuring 66 cm by 74.9 cm by 93.9 cm. A removable response panel (BRS/LVE, model TIP-001), measuring 56 cm by 21.5 cm by 45 cm, was attached to the side of each subject's cage during the experimental session. Three response keys (BRS/LVE, press plate model PPC-012) were centered and aligned horizontally on the panel. The keys were spaced 11.5 cm apart, center to center, and 51.5 cm from the cage floor. Each key required a minimum force of 0.29 N for activation. An in-line projector (BRS/LVE, model IC 901-696), mounted behind each key, could project colors and geometric forms onto the key. A yellow pilot lamp (1.2 cm in diameter) was mounted 22.5 cm to the right and 17 cm up from the center of the right-hand key. A press on this lamp (0.34 N minimum force) closed a switch on which it was mounted. A food pellet aperture (5.5 cm in diameter) was located 15.5 cm to the right and 8 cm down from the center of the right-hand key. The response panels were connected to solid-state scheduling and recording equipment located in an adjacent room.

Procedure

Baseline. A multiple schedule with learning and performance components served as the baseline. During the learning component, one of four geometric forms (horizontal line, triangle, vertical line, circle) was projected onto a red background on all three response keys. The subject's task was to learn a four-response chain by pressing the correct key in the presence of each form, e.g., horizontal line—Left correct; triangle—Right correct; vertical line—Center correct; circle—Right correct. When the chain was completed, the keylights turned off and the yellow lamp over the food pellet aperture was illuminated. A press on the yellow lamp then reset the chain. The four-response chain was maintained by food presentation under a fixed-ratio (FR 5) schedule; i.e., every fifth completion of the chain produced a food pellet (500 mg) when the yellow lamp was pressed. When the subject pressed 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 stimuli on the keys after the timeout were the same as before the timeout.

To establish a steady state of repeated acquisition, the four-response chain in the learning component 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 [8]. An example of a typical set of six chains is as follows: Left-Right-Center-Right (LRCR), CLRL, LRLC, RCRL, CLCR, RCLC; the order of the associated forms was always the same: horizontal line, triangle, vertical line, circle (reinforcement).

During the performance component of the multiple schedule, the four geometric forms were projected on a green background and the four-response chain remained the same (LCLR) from session to session. In all other aspects (FR 5 schedule of food reinforcement, timeout duration of 5 sec, etc), the performance component was identical to the learning component.

Sessions were conducted daily, Monday through Friday. Each session began in the learning component, which then alternated with the performance component after 10 reinforcements or 15 min, whichever occurred first. Each session was terminated after 100 reinforcements or 2 hr, whichever occurred first. The data for each session were analyzed in terms of (a) the overall response rate (total responses/min, excluding timeouts) in each component and (b) the overall accuracy or percent errors ((errors/total responses) $\times$ 100) in each component. In addition to these measures based on session totals, within-session changes in responding were monitored by a cumulative recorder. For example, acquisition of the response chain in the learning component was indicated by within-session error reduction, i.e., a decrease in the frequency of errors (per reinforcement) as the session progressed.

Drug testing. Dose-effect data were first obtained for phencyclidine hydrochloride. The drug was dissolved in saline and injected IM (*gluteus m.*) 5 min presession. The doses of phencyclidine were tested in a mixed order and there were generally two determinations for all of the effective doses and for the highest ineffective dose. Next, 3 mg/kg of pentobarbital sodium was administered alone. This drug was dissolved in a vehicle containing propylene glycol (40% v/v), alcohol (10% v/v), and sterile water (q.s. ad.). Pentobarbital was injected IM either 15 min (Monkeys EV and B) or 30 min (Monkey EL) presession; prior research (see *Subjects*) had indicated that the longer presession injection time for Monkey EL was necessary in order to obtain effects of pentobarbital at the beginning of the session. Varying doses of phencyclidine (in a mixed order) were then administered (IM, 5 min presession) in combination with the 3 mg/kg dose of pentobarbital (IM, 15 or 30 min presession). Two determinations were generally made for all of the effective dose combinations. The 3 mg/kg dose of pentobarbital was then administered alone again. Next, using the same testing procedure, a higher dose of pentobarbital, either 7.5 mg/kg (Monkeys EV and B) or 10 mg/kg (Monkey EL), was administered alone and in combination with varying doses of phencyclidine; prior research (see *Subjects*) had indicated that Monkey EL was less sensitive than the other two sub-

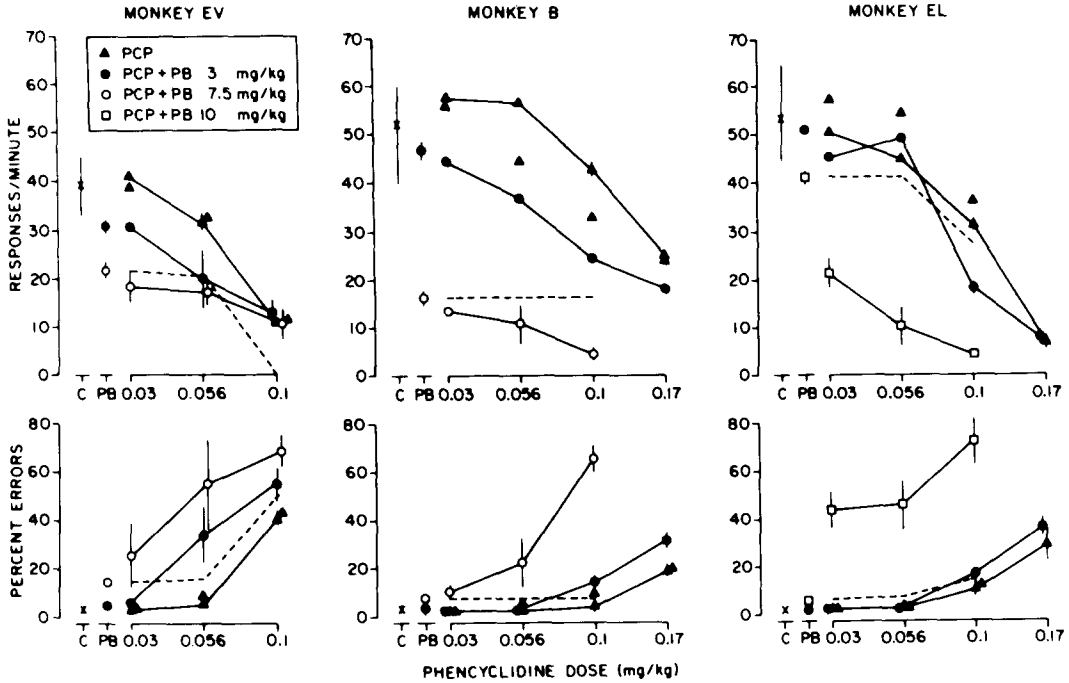

FIG. 1. Effects of phencyclidine (PCP) and pentobarbital (PB), alone and in combination, on the overall response rate and percent errors in the learning component of the multiple schedule for each subject. The points with vertical lines at C indicate the mean and range for 18 to 20 control sessions; the points without vertical lines at C (percent errors) indicate that the range is encompassed by the point. The control sessions consisted of 14 or 15 saline sessions, 2 to 4 vehicle sessions, and 1 or 2 saline + vehicle 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. Note that 7.5 mg/kg of pentobarbital was tested in Monkeys EV and B, whereas the 10 mg/kg dose was tested in Monkey EL. 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 (7.5 or 10 mg/kg) were additive.

jects to the effects of pentobarbital alone. Finally, the dose-effect data for phencyclidine alone were redetermined.

When phencyclidine and 3 mg/kg of pentobarbital were tested alone and in combination, drug sessions were generally conducted on Tuesdays and Fridays, with control sessions (saline, 5 min presession, and/or vehicle, 15 or 30 min presession, injected IM) occurring on Thursdays, and baseline sessions (no injections) on Mondays and Wednesdays. When the higher doses of pentobarbital (7.5 and 10 mg/kg) were tested alone and in combination with phencyclidine, drug sessions were generally conducted on Wednesdays, with control sessions occurring on Tuesdays, and baseline sessions on Mondays, Thursdays, and Fridays. The volume of each injection was 0.05 ml/kg 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 in the learning component of the multiple schedule for each subject. When phencyclidine was administered alone, the response rate decreased and the percent errors increased with increasing doses. When 3 mg/kg of pentobarbital, which had little or no effect when given alone, was administered in combination with phencyclidine, the dose-effect curves were generally shifted to the left relative to those for phencyclidine alone. In other words, with some exceptions (e.g., response rate at the highest dose of phencyclidine in Monkeys EV and EL), this combination of pentobarbital and phencyclidine produced greater rate-decreasing and error-increasing effects than those produced by phencyclidine alone. Note that at the highest dose of phencyclidine in Monkey EV, even though the rate-decreasing effect was essentially the same regardless of whether phencyclidine was administered alone or in combination with 3 mg/kg of pentobarbital, the phencyclidine-pentobarbital combination produced a greater error-increasing effect. When the higher doses of pentobarbital (7.5 mg/kg in Monkeys EV and B and 10 mg/kg in Monkey EL) were administered alone, the response rate decreased and the percent errors increased in all three subjects, though the rate-decreasing effect was relatively small in Monkey EL and the

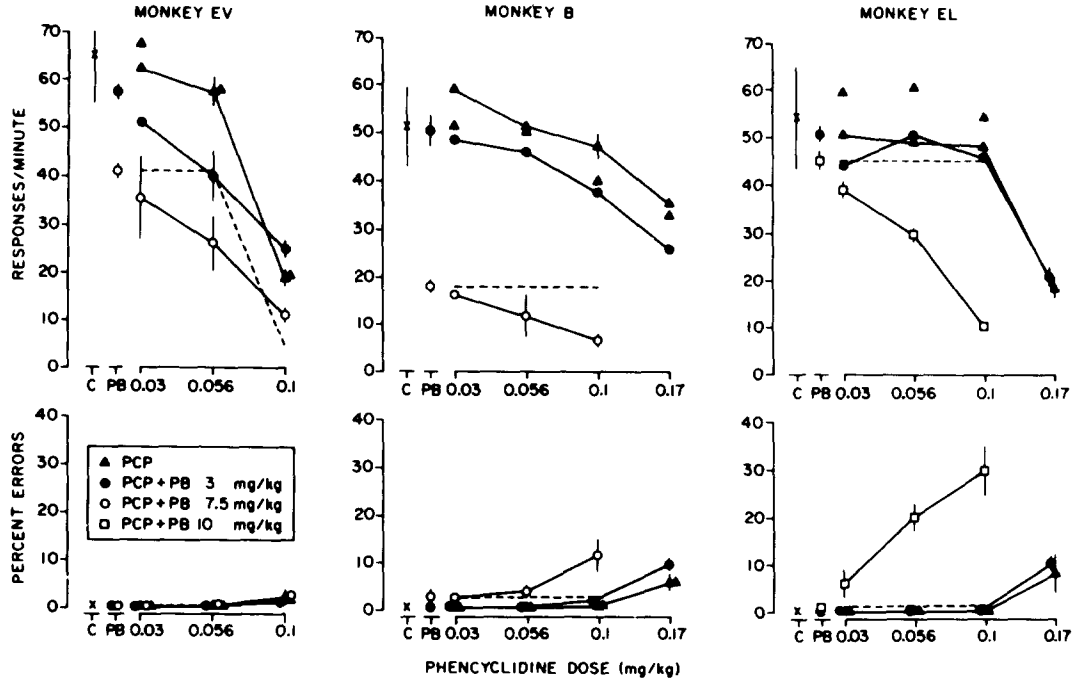

FIG. 2. Effects of phencyclidine (PCP) and pentobarbital (PB), alone and in combination, on the overall response rate and percent errors in the performance component of the multiple schedule for each subject. Abbreviated key: C=control; PB=pentobarbital alone; unconnected triangles=redetermination for phencyclidine alone; dashed lines=sum of the effects of phencyclidine alone and pentobarbital alone (7.5 or 10 mg/kg). For other details, see legend for Fig. 1.

error-increasing effect was relatively small in Monkeys B and EL. The higher doses of pentobarbital in combination with phencyclidine generally shifted the phencyclidine dose-effect curves further to the left than did the 3 mg/kg dose of pentobarbital. A notable exception was the convergence of the dose-effect curves for rate (but not for accuracy) at the highest dose of phencyclidine in Monkey EV. 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 (7.5 or 10 mg/kg) were additive. 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 [7]. 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. [3]). 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 (7.5 or 10 mg/kg) were administered in combination, the effects on rate and accuracy were generally greater than expected from simple addition of the effects of each drug given alone. The only exception occurred at the highest dose of phencyclidine in Monkey EV, where the rate-decreasing effect of the phencyclidine-pentobarbital combination was less than additive.

Figure 2 shows the effects of phencyclidine and pentobarbital, alone and in combination, on the overall response rate and percent errors in the performance component of the multiple schedule for each subject. A comparison of Fig. 2 with Fig. 1 indicates that the drug effects in the performance component were generally similar to those obtained in the learning component. There was, however, a differential sensitivity to the drug effects between the two components. For example, when phencyclidine was administered alone and in combination with pentobarbital in Monkey EV, there was little or no effect on percent errors in the performance component, whereas a dose-dependent error-increasing effect was obtained in the learning component (note that the two components have different scales on the ordinate for percent errors). In Monkey B, the combination of 0.1 mg/kg of phencyclidine and 3 mg/kg of pentobarbital had a greater rate-decreasing effect in the learning component than in the performance component, even though neither of these doses alone had an effect on rate in either component. In Monkey EL, 10 mg/kg of pentobarbital alone had a rate-decreasing

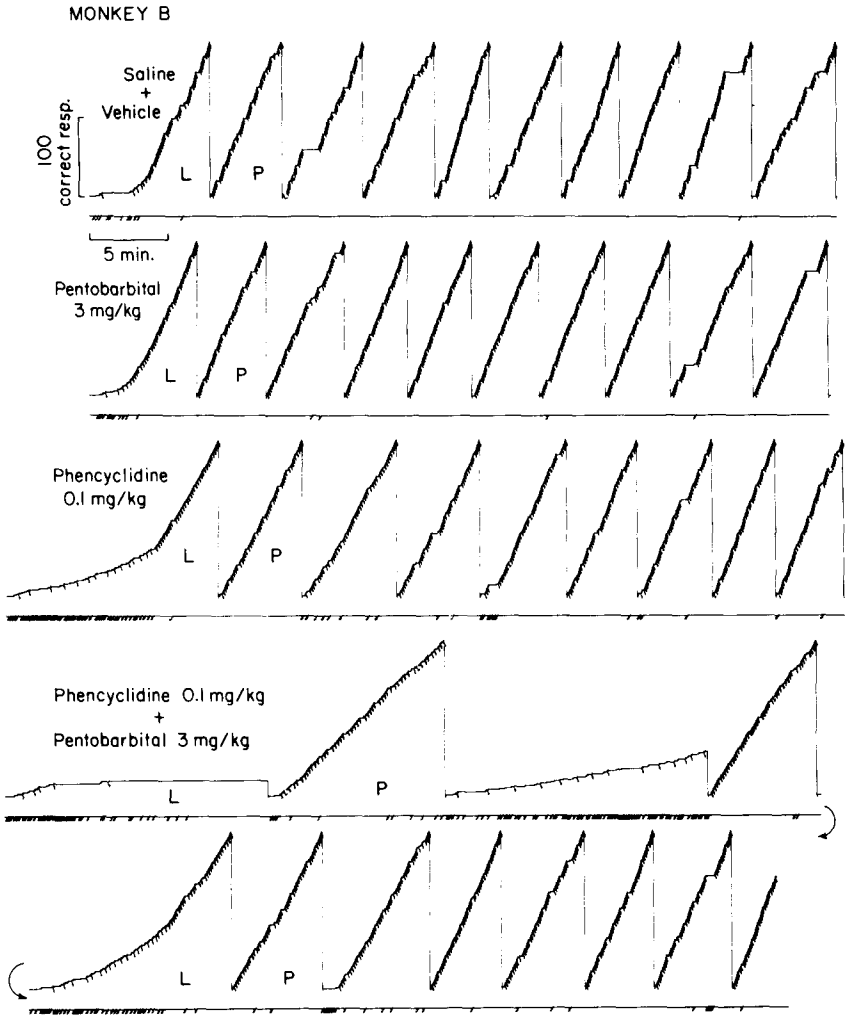

FIG. 3. Cumulative records for Monkey B showing the pattern of responding under a multiple schedule with learning (L) and performance (P) components during a representative control session (saline + vehicle) and during sessions preceded by injections of pentobarbital (3 mg/kg) and phencyclidine (0.1 mg/kg), alone and in combination. Each record represents a complete session (either 100 reinforcements or 2 hr), except at phencyclidine 0.1 mg/kg, where the last performance component has been omitted. 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. A change in components of the multiple schedule reset the stepping pen.

effect in the learning component but not in the performance component. When 0.1 mg/kg of phencyclidine was administered alone and in combination with 3 mg/kg of pentobarbital in Monkey EL, there was no effect on rate or accuracy in the performance component, whereas rate-decreasing and error-increasing effects were obtained in the learning component. In summary, in all three subjects the performance component tended to be less sensitive than the learning component to the drug effects.

Figure 3 shows the pattern of responding during a representative control session (one that approximated the mean for both overall response rate and overall accuracy) and during several drug sessions for Monkey B. In the control record (top), errors decreased in frequency in the learning component as the session progressed; i.e., acquisition occurred. After the first 4 min of this session, correct responding occurred at a relatively high rate in both components and virtually no errors were made. When 3 mg/kg of pentobarbital was administered alone, the pattern of responding was essentially the same as that seen in the control session. When 0.1 mg/kg of phencyclidine was administered alone, there was a clear error-increasing effect in the learning com-

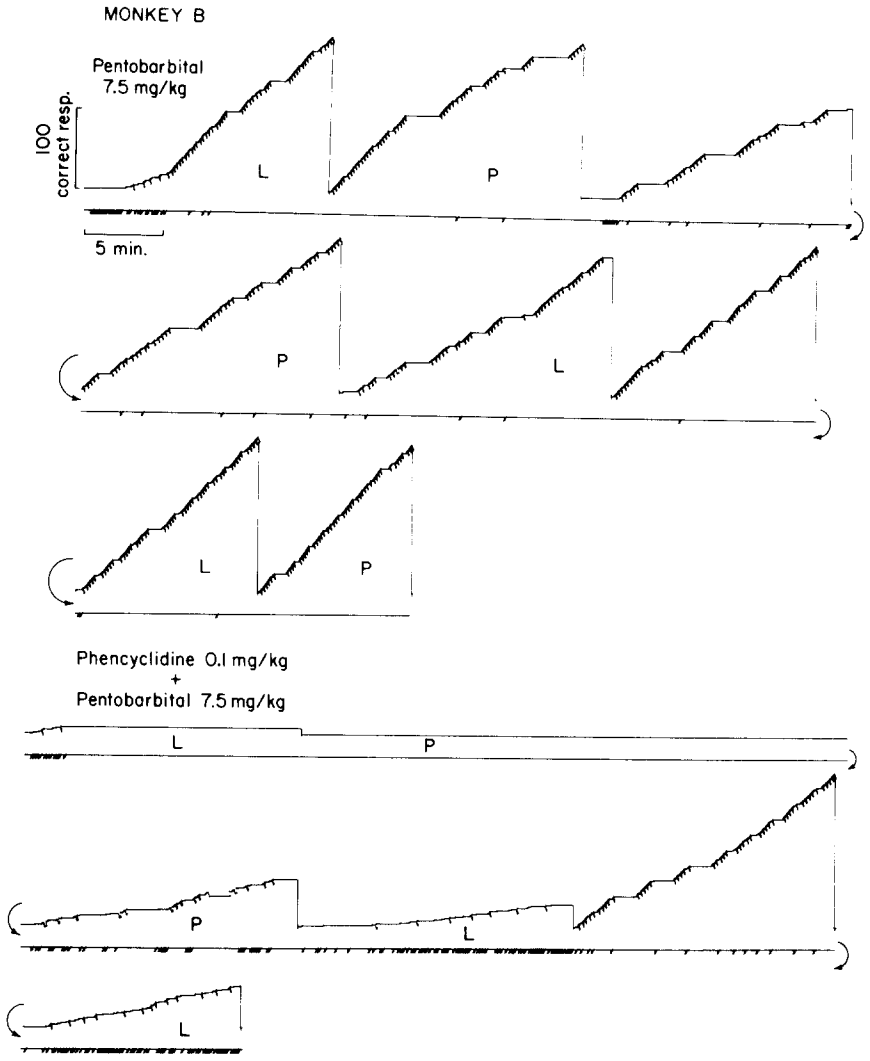

FIG. 4. Cumulative records for Monkey B showing the pattern of responding under a multiple schedule with learning (L) and performance (P) components during two high-dose pentobarbital sessions: 7.5 mg/kg of pentobarbital alone and 0.1 mg/kg of phencyclidine in combination with 7.5 mg/kg of pentobarbital. Each record represents a complete session. The recording details are the same as in Fig. 3.

ponent, although within-session error reduction (acquisition) still occurred; the frequency of errors in the performance component remained near zero. In contrast, when this dose of phencyclidine was administered in combination with 3 mg/kg of pentobarbital, responding was disrupted in both components. During the first learning component, the rate of correct responding was greatly decreased and errors were relatively frequent. When the schedule then changed to the performance component, the rate of correct responding increased substantially, although the rate was noticeably lower and the frequency of errors was somewhat higher than control. As the session progressed, the rate-decreasing and error-increasing effects in both components diminished, with the pattern of responding in the performance component returning to control more quickly than that in the learning component.

Figure 4 shows the within-session effects of 7.5 mg/kg of pentobarbital alone and in combination with 0.1 mg/kg of phencyclidine on the responding of Monkey B. When 7.5 mg/kg of pentobarbital was administered alone, the rate of correct responding in both components was substantially decreased in comparison to control (Fig. 3, top), with frequent periods of pausing occurring throughout the session. This large rate-decreasing effect was accompanied by a small error-increasing effect in both components. When 7.5 mg/kg of pentobarbital was administered in combination with 0.1 mg/kg of phencyclidine, both the rate-decreasing and error-increasing effects were more pronounced. After a long initial

pause in both components, the subject began responding in the performance component; the rate of correct responding was very low and errors were frequent. When the schedule then changed to the learning component, the rate of correct responding decreased even more and many errors occurred. During the last cycle of the multiple schedule, the pattern of responding in the performance component resembled that seen with this dose of pentobarbital alone (top), whereas the large effects on rate and errors in the learning component persisted. In general, the within-session effects of phencyclidine and pentobarbital, alone and in combination, in Monkey B (Figs. 3 and 4) were replicated with the other two subjects, although the particular doses and the magnitude of the effects varied.

DISCUSSION

In the present study, the higher doses of phencyclidine and pentobarbital, when administered alone, generally decreased the overall response rate and increased the percent errors in both components of the multiple schedule. The performance component tended to be less sensitive than the learning component to the drug effects. These results are consistent with previous research showing that phencyclidine and pentobarbital, when administered alone, produce similar dose-related disruptive effects on complex operant behavior, e.g., the acquisition and performance of conditional discriminations in patas monkeys [7], oddity-discrimination performance in rhesus monkeys [2] and matching-to-sample performance in pigeons [6].

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 (Figs. 1 and 2). The shift in the dose-effect curves 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. [5]). This interpretation is supported by the finding that, in two of three monkeys, combinations of phencyclidine with a high dose of pentobarbital (7.5 or 10 mg/kg) consistently produced greater rate-decreasing and error-increasing effects than expected from simple addition of the effects of each drug given alone.

The present finding that phencyclidine-pentobarbital combinations produced supra-additive effects on response rate is clearly at odds with the results reported by Chait and Balster [3]. In that study, phencyclidine and pentobarbital generally interacted antagonistically in squirrel monkeys responding under a variable-interval schedule of food presentation. Chait and Balster [3] suggested that such an interaction may be species-dependent since other research [1,4], 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. 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 [10]. The generality of these findings in rhesus monkeys is extended by the present research, which involved complex schedule-controlled behavior in a different genus of *cercopithecidae*, the patas monkey.

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