1-1-1983

DRUG EFFECTS ON REPEATED ACQUISITION: COMPARISON OF CUMULATIVE AND NON-CUMULATIVE DOSING

Donald M. Thompson
Georgetown University

Joseph M. Moerschbaecher
Georgetown University

Peter J. Winsauer
Georgetown University

Recommended Citation

Thompson, D., Moerschbaecher, J., & Winsauer, P. (1983). DRUG EFFECTS ON REPEATED ACQUISITION: COMPARISON OF CUMULATIVE AND NON-CUMULATIVE DOSING. *Journal of the Experimental Analysis of Behavior, 39* (1), 175-184. https://doi.org/10.1901/jeab.1983.39-175

JOURNAL OF THE EXPERIMENTAL ANALYSIS OF BEHAVIOR 1983, 39, 175-184 NUMBER 1 (JANUARY)

DRUG EFFECTS ON REPEATED ACQUISITION: COMPARISON OF CUMULATIVE AND NON-CUMULATIVE DOSING

DONALD M. THOMPSON, JOSEPH M. MOERSCHBAECHER, AND PETER J. WINSAUER

GEORGETOWN UNIVERSITY SCHOOLS OF MEDICINE AND DENTISTRY

Pigeons acquired a different four-response chain each session by responding sequentially on three keys in the presence of a sequence 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. Each day there were four 15-minute sessions, with a 10-minute intersession interval. Cumulative dose-effect curves for phencyclidine, pentobarbital, and *d*-amphetamine were obtained by giving an injection before each of the four sessions; successive injections increased the cumulative dose in equally spaced logarithmic steps. For comparison, non-cumulative doses of each drug (i.e., doses not preceded by other doses on the same day) were also tested. As the cumulative dose of each drug increased, the overall response rate decreased, the percent errors increased, and there was less within-session error reduction (acquisition). With phencyclidine and pentobarbital, the rate-decreasing and error-increasing effects tended to be greater with a non-cumulative dose than with the corresponding cumulative dose. In contrast, with *d*-amphetamine, the effects were considerably greater with the cumulative doses. The results indicate that although the cumulative-dosing procedure saved a substantial amount of time in determining dose-effect curves, there were quantitative differences in effects between cumulative and non-cumulative doses.

Key words: repeated acquisition, response chains, fixed-ratio schedule, cumulative dosing, phencyclidine, pentobarbital, *d*-amphetamine, key peck, pigeons

In the study of drugs with operant techniques, a practical problem is the considerable length of time usually required to obtain dose-effect curves. Typically, a complete session is devoted to measuring the behavioral effects of a given dose, and the drug sessions are spaced several days apart to minimize "carry-over" effects (Boren, 1966). As an alternative to this time-consuming approach, Boren (1966) suggested the use of a cumulative-dosing procedure. With this procedure, multiple doses can be tested in a single day, with each successive dose being larger than the preceding one. For example, Hanson, Witoslawski, Campbell, and Itkin (1966) used such a procedure to obtain dose-effect data for chlorpromazine in squirrel monkeys responding under a Sidman avoidance schedule. The behavioral effects of five oral doses were assessed during a single 7-hr session, with the first dose given 30 min before the session and the remaining doses administered at 90-min intervals. Chlorpromazine produced a graded decrease in the rate of responding as the cumulative dose increased; similar results were found with two other phenothiazines and with haloperidol and pentobarbital.

More recently, cumulative-dosing procedures have been used to assess the effects of a variety of drugs on fixed-ratio (FR) performance maintained by food presentation. For example, Kelleher and Goldberg (1979) reported that increasing cumulative doses of morphine or naloxone decreased the overall rate of FR responding in rhesus monkeys. Similar results have been found with cumulative doses of naltrexone in squirrel monkeys (Spealman, Kelleher, Morse, & Goldberg, 1981). Wenger (1980) obtained cumulative dose-effect curves for phencyclidine, ketamine, pentobarbital, *d*-amphetamine, and morphine in mice. Each drug decreased the overall rate of FR responding as the cumulative dose increased. Wenger also found that a non-cumulative dose of each drug (i.e., a dose that was not preceded by other doses on the same day) produced essentially the same effect as the corresponding cumulative dose.

In another study that compared the behavioral effects of cumulative and non-cumulative

This work 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, D.C. 20007.

doses, "pigeons were trained to track different key colors, depending on whether they had been injected with phencyclidine or saline prior to the session" (McMillan, Cole-Fullenwider, Hardwick, & Wenger, 1982, p. 143). Differential responding was maintained by food presentation under a second-order FR schedule. Other doses, either cumulative or non-cumulative, were then substituted for the training dose. With regard to the percent of FRs completed on the key appropriate for phencyclidine, the cumulative and non-cumulative dose-effect curves were almost identical when the data were averaged across subjects, though there were marked individual differences.

In the present research, a cumulative-dosing procedure was used to provide a rapid evaluation of drug effects on complex operant behavior in pigeons. More specifically, cumulative dose-effect curves were obtained for phencyclidine, pentobarbital, and *d*-amphetamine in a repeated-acquisition task, where sequential responding on three keys was maintained under an FR schedule. For comparison, non-cumulative doses of each drug were also tested.

METHOD

Subjects

Two adult male White Carneaux pigeons were maintained at approximately 80% of their free-feeding body weights by food presented during the sessions and by supplemental feeding after the last session each day. The 80% values were 450 g and 440 g for P-7865 and P-2252, respectively. 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 (Thompson & Moerschbaecher, 1981).

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 .18 N for activation. Each key could be transilluminated by three Sylvania 24-ESB 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" (which appeared yellow-orange to the experimenters) was produced by the red and green lights being on simultaneously. Electromechanical programming and recording equipment was used. 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. This type of sequential responding is procedurally defined as a "chain" because each response (except the last) produces a discriminative stimulus controlling the response that follows (Kelleher, 1966; Thompson, 1975). The same chain (in this case, Left-Right-Center-Right or LRCR) was repeated throughout a given session. Responding was maintained by food presentation under a second-order FR schedule (an FR 5 schedule with FR 4 components); i.e., every fifth completion of the four-response chain was followed by 5-sec 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 .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.

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 (see Thompson, 1973). 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.

There were four 15-min sessions each day (Monday through Friday), with a 10-min inter-

session interval, during which time the chamber was dark (the first session was also preceded by a 10-min blackout). 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 repeated-acquisition baseline was stabilized. The baseline was considered stable when the response rate and the percent errors no longer showed systematic change from session to session. After baseline stabilization (four sessions per day for 30 days), cumulative dose-effect data were obtained for phencyclidine hydrochloride. The drug was dissolved in saline (.9%) and injected intramuscularly at the start of each blackout period (i.e., 10 min before the session); successive injections increased the cumulative dose by ¼ log-unit steps. More specifically, .32 mg/kg of phencyclidine was injected before the first session, .24 mg/kg (producing a cumulative dose of .56 mg/kg) was injected before the second session, .44 mg/kg (producing a cumulative dose of 1 mg/kg) was injected before the third session, and .8 mg/kg (producing a cumulative dose of 1.8 mg/kg) was injected before the fourth session. As a control, saline was injected intramuscularly 10 min before each of the four sessions on another day. After the cumulative dose-effect curves for phencyclidine had been determined twice in each subject, two non-cumulative doses of phencyclidine (.56 and 1 mg/kg) were tested. To permit a comparison with the corresponding cumulative dose across the same time period, the .56 mg/kg dose was injected 10 min before the second session on one day, and the 1 mg/kg dose was injected 10 min before the third session on another day; saline was injected 10 min before each of the other three sessions on these days. The cumulative dose-effect curves for phencyclidine were then redetermined. Pentobarbital sodium and *d*-amphetamine sulfate (dissolved in saline) were then tested, in that order, using the same procedure as that described for phencyclidine, except for variations in the range of cumulative doses and the number of non-cumulative doses tested.

Throughout testing, drug (or saline) sessions were generally conducted on Tuesdays and Fridays, with baseline sessions (no injections) occurring on Mondays, Wednesdays, and Thursdays. Approximately one week of baseline sessions intervened between the end of a series of injections with one drug and the start of a series with another. The volume of each injection was .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 cumulative and non-cumulative doses of phencyclidine on the

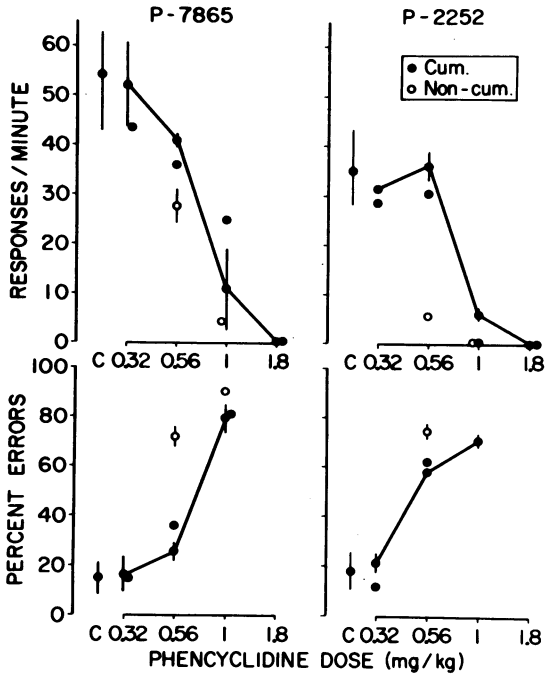

Fig. 1. Effects of cumulative and non-cumulative doses of phencyclidine on the overall response rate and overall accuracy for each pigeon. The points and vertical lines at C indicate the mean and range for 8 to 12 control (saline) sessions. The points with vertical lines in the dose-effect data indicate 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. Points for percent errors have been omitted in cases where the overall response rate was virtually zero. The unconnected filled circles show a redetermination of the cumulative dose-effect data after the non-cumulative doses were tested.

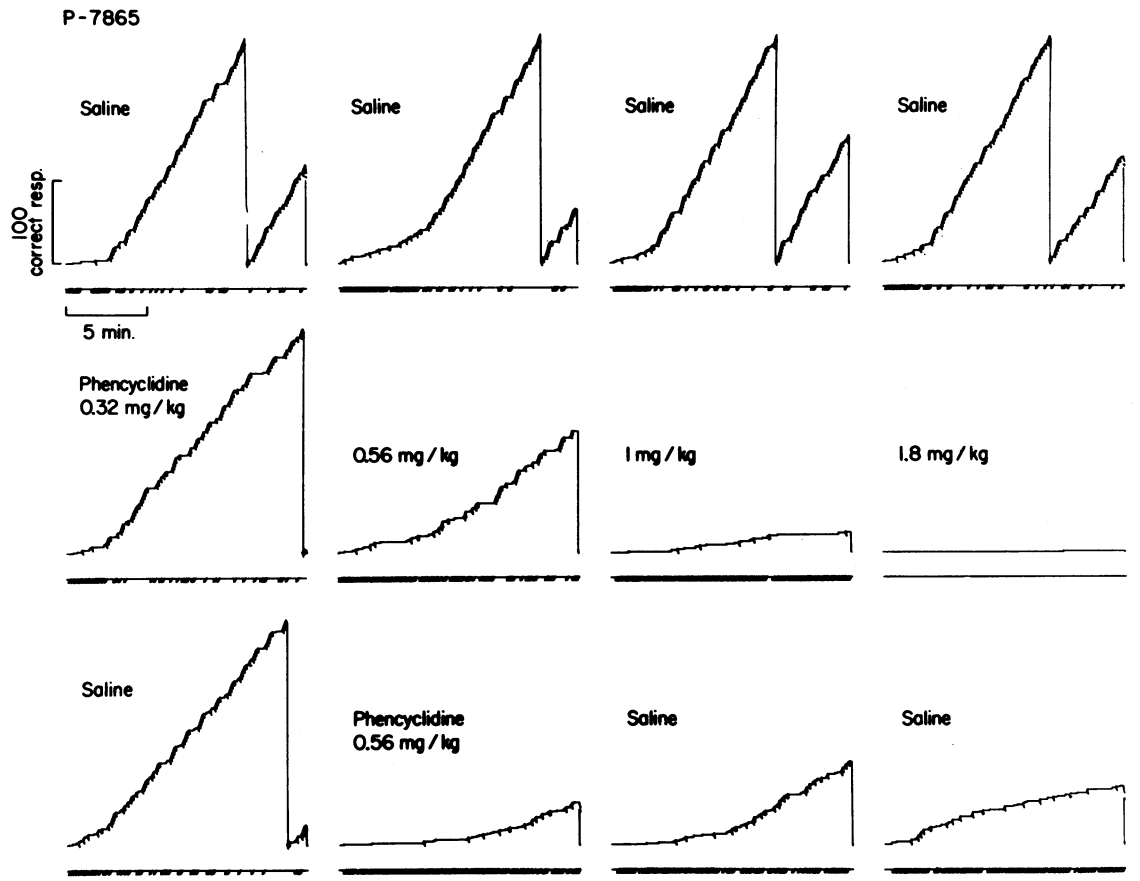

Fig. 2. Within-session effects of phencyclidine in P-7865. Each row of four cumulative records is from a different day. On each day, there were four 15-min sessions (shown left to right), each with a different four-response chain (the 10-min intersession interval is not shown to scale). The top row shows sessions that were preceded by saline injections, the middle row shows sessions that were preceded by increasing cumulative doses of phencyclidine, and the bottom row shows the effects of a non-cumulative dose, which was injected before the second session. 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.

overall response rate and overall accuracy for each subject. As the cumulative dose of phencyclidine increased, the response rate decreased and the percent errors increased. Note that in P-2252 at .56 mg/kg (cumulative), there was a large error-increasing effect but no effect on overall response rate. In general, the two non-cumulative doses of phencyclidine produced greater rate-decreasing and error-increasing effects than those produced by the corresponding cumulative doses. A notable exception occurred at 1 mg/kg in P-2252, where the overall response rate was virtually zero after both the non-cumulative dose and the cumulative dose (redetermination).

Figure 2 shows the within-session effects of phencyclidine in P-7865. The top row of cumulative records shows the pattern of responding during four saline sessions from one day. As can be seen in each of these records, errors decreased in frequency as the session progressed; i.e., acquisition occurred. After the first 5 min of each saline 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. The middle row of records shows four sessions that were preceded by increasing cumulative doses of phencyclidine. The lowest dose (.32 mg/kg) was ineffective; the pattern of

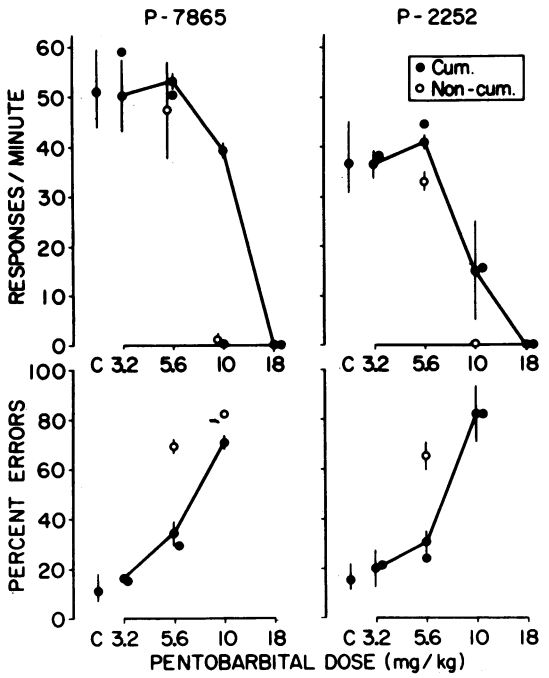

Fig. 3. Effects of cumulative and non-cumulative doses of pentobarbital on the overall response rate and overall accuracy for each pigeon. The points and vertical lines at C indicate the mean and range for 8 to 12 control (saline) sessions. The unconnected filled circles show a redetermination of the cumulative dose-effect data after the non-cumulative doses were tested. For other details, see legend for Figure 1.

responding during this session was similar to that seen in the saline sessions (e.g., the first record in the bottom row). After the second injection of phencyclidine (a cumulative dose of .56 mg/kg), the rate of correct responding was noticeably decreased in comparison to control and the relative frequency of errors was increased somewhat, though acquisition (within-session error reduction) still occurred. The third injection of phencyclidine (a cumulative dose of 1 mg/kg) produced a large decrease in the rate of correct responding and errors occurred throughout the session, with no sign of acquisition. After the fourth injection of phencyclidine (a cumulative dose of 1.8 mg/kg), there was virtually no responding during the session. The bottom row of records shows the effects of a non-cumulative dose of phencyclidine (.56 mg/kg), which was injected before the second session. This non-cumulative dose produced a greater decrease in the rate of correct responding and a greater increase in errors than did the corresponding cumulative dose. These effects continued, with little or no attenuation, during the next two sessions.

Pentobarbital dose-effect data for overall response rate and overall accuracy are shown in Figure 3. A comparison of Figure 3 with Figure 1 indicates that the effects of pentobarbital were generally similar to those obtained with phencyclidine, though there was a ten-fold difference in the range of effective doses. Pentobarbital, like phencyclidine, decreased the response rate and increased the percent errors as the cumulative dose increased. As was the case with phencyclidine, the rate-decreasing and error-increasing effects of pentobarbital tended to be greater with a non-cumulative dose than with the corresponding cumulative dose. In contrast to phencyclidine, however, there were several instances in which pentobarbital increased the percent errors without affecting the overall response rate (e.g., at 5.6 mg/kg, cumulative and non-cumulative, in both subjects).

The within-session effects of pentobarbital in P-7865 are shown in Figure 4. As the cumulative dose of pentobarbital increased (middle row of records), there was a graded decrease in the rate of correct responding, a graded increase in the frequency of errors (with a maximum at 10 mg/kg), and progressively less within-session error reduction (acquisition). When a non-cumulative dose of pentobarbital (5.6 mg/kg) was injected before the second session (bottom row of records), the effects during that session were greater than after the corresponding cumulative dose and the effects were still evident during the fourth session. In general, the within-session effects of pentobarbital (Figure 4) were quite similar to the within-session effects of phencyclidine (Figure 2).

Figure 5 shows the effects of cumulative and non-cumulative doses of *d*-amphetamine on the overall response rate and overall accuracy for each subject. *d*-Amphetamine, like phencyclidine and pentobarbital, decreased the response rate and increased the percent errors as the cumulative dose increased. However, in contrast to phencyclidine and pentobarbital, the data points for the non-cumulative doses of *d*-amphetamine were shifted to the right relative to the cumulative dose-effect curves (compare Figure 5 with Figures 1 and 3). In other words, the non-cumulative doses of *d*-amphetamine produced smaller rate-decreasing and error-increasing effects than those

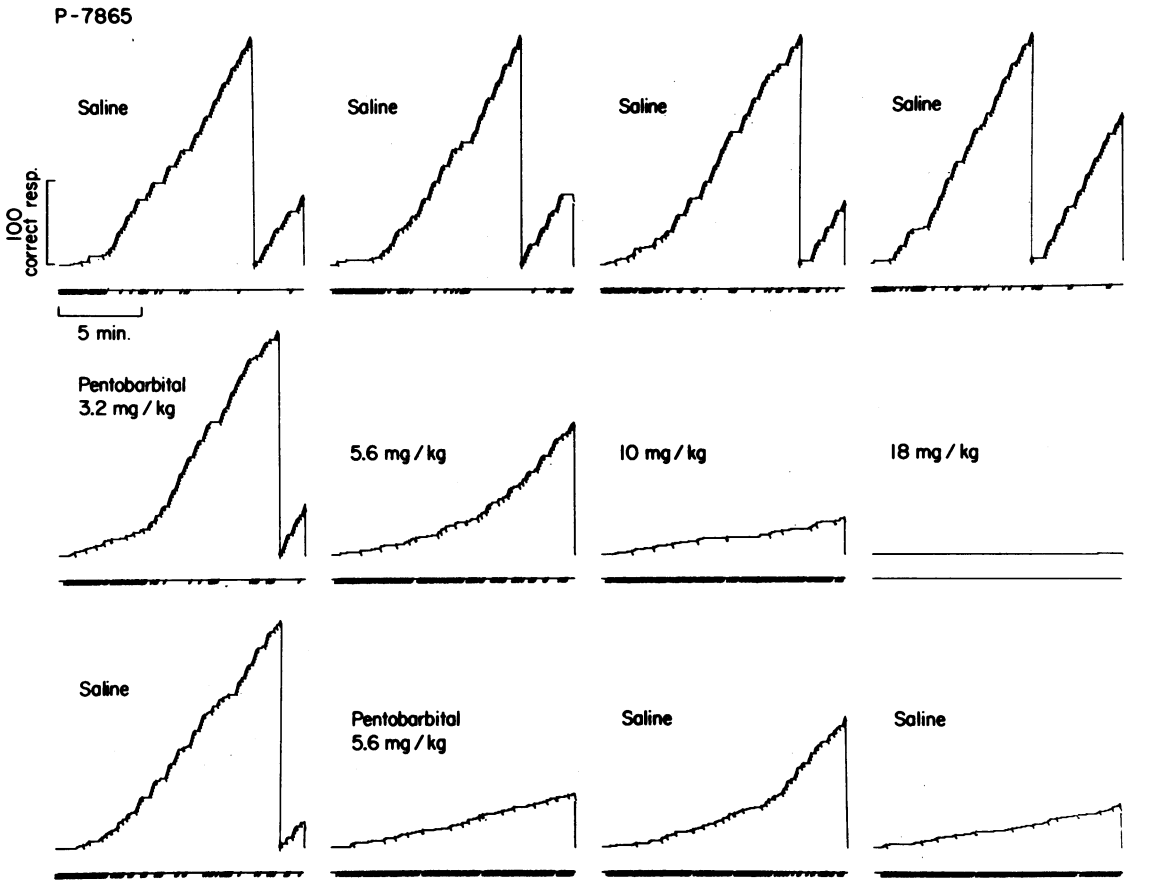

Fig. 4. Within-session effects of pentobarbital in P-7865. The top row shows sessions that were preceded by saline injections, the middle row shows sessions that were preceded by increasing cumulative doses of pentobarbital, and the bottom row shows the effects of a non-cumulative dose, which was injected before the second session. For other details, see legend for Figure 2.

produced by the corresponding cumulative doses. When the cumulative dose-effect data were redetermined (unconnected filled circles), there was generally close agreement with the original curves, except for response rate at .56 mg/kg in P-7865 and at 1.8 and 3.2 mg/kg in P-2252. In regard to selective effects on rate and accuracy, *d*-amphetamine decreased the overall response rate without affecting the percent errors in certain instances (e.g., at .32 mg/kg in P-7865) and increased the percent errors without affecting the overall response rate in other instances (e.g., at 1 mg/kg, cumulative, in P-2252). Only the latter case was seen with phencyclidine and pentobarbital.

Figure 6 shows the within-session effects of *d*-amphetamine in P-7865. The lowest effective cumulative dose was .56 mg/kg (middle row of records). This dose decreased the rate of correct responding, increased the frequency of errors, and disrupted within-session error reduction (acquisition). When the cumulative dose of *d*-amphetamine was increased to 1 mg/kg, there was a sharp drop in the overall rate of responding; all of the responses that did occur were errors. After the fourth injection (a cumulative dose of 1.8 mg/kg), there was virtually no responding during the session. In comparison to the cumulative doses of phencyclidine (Figure 2) and pentobarbital (Figure 4), the cumulative doses of *d*-amphetamine produced less graded effects on the within-session pattern of responding. When a non-cumulative dose of *d*-amphetamine (.56 mg/kg) was injected before the second session (bottom row of records), the pattern of responding during that session was similar to that seen in the saline sessions (top row). However, during the

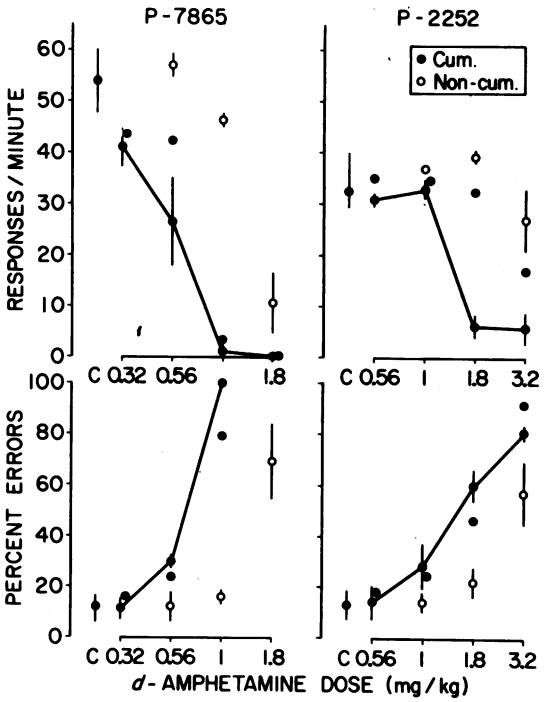

Fig. 5. Effects of cumulative and non-cumulative doses of *d*-amphetamine on the overall response rate and overall accuracy for each pigeon. The points and vertical lines at C indicate the mean and range for 8 control (saline) sessions. The unconnected filled circles show a redetermination of the cumulative dose-effect data after the non-cumulative doses were tested. For other details, see legend for Figure 1.

fourth session, which started 60 min after the .56 mg/kg dose was injected, the rate of correct responding was greatly decreased and acquisition was disrupted. This unexpected finding with *d*-amphetamine (i.e., delayed behavioral effects) was not obtained with the non-cumulative doses of phencyclidine or pentobarbital. In general, the within-session effects of phencyclidine, pentobarbital, and *d*-amphetamine in P-7865 (Figures 2, 4, and 6) were replicated with the other subject, although the particular doses (with *d*-amphetamine) and the magnitude of the effects varied.

DISCUSSION

The present research examined the applicability of cumulative dosing to the assessment of drug effects on complex operant behavior. A repeated-acquisition procedure that had previously been used in several drug studies with pigeons (e.g., Thompson & Moerschbaecher, 1979b) was modified by decreasing the session duration and by conducting four sessions per day (each with a different response chain) instead of only one session per day. Despite these modifications, acquisition (error reduction) occurred during each control session and the pattern of acquisition was similar from session to session (Figures 2, 4, and 6, top). The present study showed that this repeated-acquisition baseline was sensitive to the effects of cumulative doses of phencyclidine, pentobarbital, and *d*-amphetamine. As the cumulative dose of each drug increased, the overall response rate decreased, the percent errors increased, and there was less within-session error reduction (acquisition). These drug effects are qualitatively similar to those previously found with non-cumulative doses of phencyclidine, pentobarbital, and *d*-amphetamine in pigeons responding in a repeated-acquisition task (e.g., Thompson & Moerschbaecher, 1980, 1981). The time required to test the drugs, however, was substantially reduced in the present study. Instead of testing only two doses per week, a dose-effect curve could be obtained in a single day with the cumulative-dosing procedure.

One might argue that the error-increasing effect of the drugs was due to their rate-decreasing effect since acquisition requires exposure to the reinforcement contingencies, and the lowering of response rate by a drug would prevent the subject from getting the necessary exposure. However, there were several instances in the present data where a drug increased the percent errors without affecting the overall response rate (e.g., see Figure 3: 5.6 mg/kg, cumulative, in both subjects). There was also a case in which a drug decreased response rate somewhat without affecting accuracy (see Figure 5: .32 mg/kg in P-7865). Moreover, previous research with repeated-acquisition baselines has shown that certain drugs, such as naloxone (Thompson & Moerschbaecher, 1981), and behavioral manipulations, such as prefeeding (Thompson & Moerschbaecher, 1979a), can produce substantial rate-decreasing effects that are not accompanied by error-increasing effects. It would seem, therefore, that accuracy is not necessarily related to rate.

When non-cumulative doses of each drug were tested in the present study, the effects on overall response rate and overall accuracy were qualitatively similar to the effects produced by the corresponding cumulative doses. There

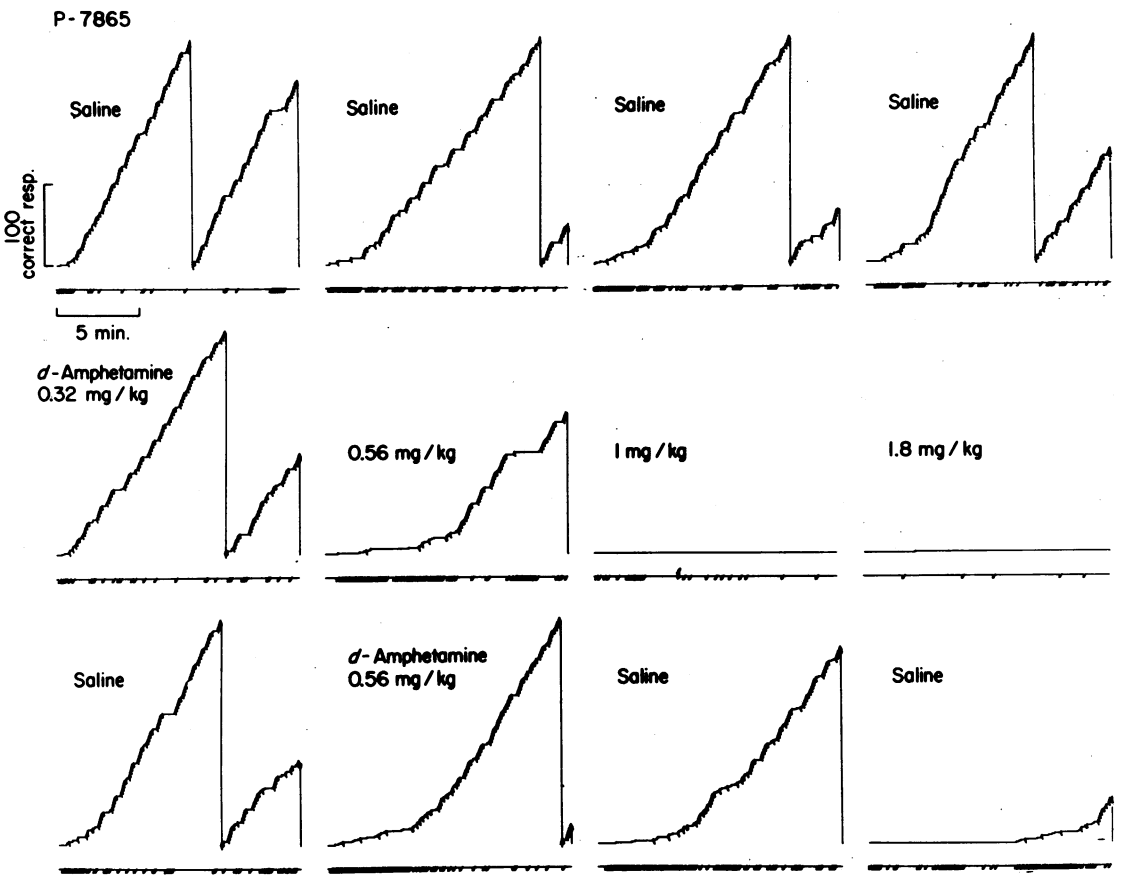

Fig. 6. Within-session effects of *d*-amphetamine in P-7865. The top row shows sessions that were preceded by saline injections, the middle row shows sessions that were preceded by increasing cumulative doses of *d*-amphetamine, and the bottom row shows the effects of a non-cumulative dose, which was injected before the second session. For other details, see legend for Figure 2.

were, however, some apparent quantitative differences in effects between the two dosing procedures; the nature of the difference depended on the drug. With phencyclidine and pentobarbital, the rate-decreasing and error-increasing effects tended to be greater with a non-cumulative dose than with the corresponding cumulative dose. In contrast, with *d*-amphetamine, the effects were considerably greater with the cumulative doses. That phencyclidine and pentobarbital were similar to each other but differed from *d*-amphetamine in this regard could not have been predicted on the basis of results obtained with less complex schedule-controlled behavior. For example, Wenger (1976) reported that non-cumulative doses of phencyclidine and *d*-amphetamine produced similar effects, which differed from those of pentobarbital, in pigeons responding on a single key under a multiple FR FI schedule of food presentation. The present finding that the data points for the non-cumulative doses of *d*-amphetamine were shifted to the right relative to the cumulative dose-effect curves cannot be attributed to the development of behavioral tolerance since the cumulative dose-effect data were generally replicated after the non-cumulative doses were tested.

The present finding that cumulative and non-cumulative doses produced quantitatively different effects is not in agreement with the results reported by Wenger (1980). In that study, the overall rate of FR responding in mice decreased as the cumulative dose of phencyclidine, pentobarbital, or *d*-amphetamine increased. Wenger reported that a non-cumula-

tive dose of each drug produced an effect that was "identical" to that produced by the corresponding cumulative dose. The discrepancy between the results of the two studies may be related to several methodological differences. Apart from the obvious difference in the species used and in the complexity of the baseline, the two studies also differed in terms of data analysis and the cumulative-dosing procedure. Unlike the present research, the cumulative dose-effect curves in Wenger's experiment were based on group data. It has been shown in a recent study of phencyclidine discrimination in pigeons (McMillan et al., 1982) that group data may obscure quantitative differences in behavioral effects between cumulative and non-cumulative doses in individual subjects. In the present research, the cumulative doses referred to the total amount of drug injected on a given day, and the time between successive injections was constant. In Wenger's study, however, the "cumulative" doses referred to the amount of drug actually injected each time, and the inter-injection interval could vary.

As Boren (1966) pointed out, if a drug has a rapid onset of action and a long duration, then the effect of a cumulative dose should approximate the effect of the corresponding non-cumulative dose. For example, if the first injection was 1 mg/kg and the second injection was 2 mg/kg (producing a cumulative dose of 3 mg/kg), then the effect obtained after the second injection should be similar to that produced by a single injection of 3 mg/kg. The same type of reasoning was used in designing the present experiment, but the results showed quantitative differences in effects between the two dosing procedures, especially with *d*-amphetamine. These differences may be related to the pharmacokinetics (onset, duration, etc.) of the drugs studied.

In the present experiment, the effects of the non-cumulative doses provide some information about each drug's time course. A good example is the unexpected finding obtained with .56 mg/kg of *d*-amphetamine in P-7865 (Figure 6, bottom row). Although this dose was injected 10 min before the second session, its behavioral effects were not clearly seen until the fourth session, which started 60 min after the injection. This finding was reliable; it was replicated in P-7865, and similar delayed behavioral effects were found in the other subject when 1 mg/kg of *d*-amphetamine (non-cumulative) was injected before the second session. These results would seem to be relevant to *d*-amphetamine's effects in the cumulative-dosing procedure. For example, with regard to the data shown in Figure 6 (middle row), if the .32 mg/kg dose produced delayed effects, this might partially explain why there was a sharp decrease in the overall response rate after the cumulative dose was increased to 1 mg/kg. The results also complement a previous finding reported by Gonzalez and Goldberg (1977). In that study, a high dose of *d*-amphetamine (injected intramuscularly) produced a delayed rate-increasing effect in a monkey responding under a second-order schedule of food presentation during an extended session.

As an alternative to the pharmacokinetic interpretation, the present results with *d*-amphetamine may reflect a drug-environment interaction. For example, in regard to the data shown in Figure 6, the behavior during the fourth session (bottom row) may have been disrupted by *d*-amphetamine because a number of reinforcers had already been presented by that time. Regarding phencyclidine and pentobarbital, the shift to the right in the cumulative dose-effect curves, relative to the data points for the non-cumulative doses, may indicate the development of acute behavioral tolerance during the cumulative dosing. One would expect such tolerance to develop since the rate-decreasing and error-increasing effects at intermediate doses would necessarily decrease reinforcement density (cf. Schuster, Dockens, & Woods, 1966). Although this account seems reasonable, the question remains as to why acute behavioral tolerance did not develop to cumulative doses of *d*-amphetamine.

In summary, the present study showed that a cumulative-dosing procedure saved a substantial amount of time in determining dose-effect curves for phencyclidine, pentobarbital, and *d*-amphetamine in pigeons responding in a repeated-acquisition task. The effects of the cumulative doses on rate and accuracy were qualitatively similar to the effects produced by non-cumulative doses. On the other hand, there were some apparent quantitative differences in effects between the two dosing procedures that may be related to pharmacokinetic variables and/or acute behavioral tolerance.

REFERENCES

Boren, J. J. The study of drugs with operant techniques. In W. K. Honig (Ed.), *Operant behavior: Areas of research and application*. New York: Appleton-Century-Crofts, 1966.

Gonzalez, F. A., & Goldberg, S. R. Effects of cocaine and *d*-amphetamine on behavior maintained under various schedules of food presentation in squirrel monkeys. *Journal of Pharmacology and Experimental Therapeutics*, 1977, **201**, 33-43.

Hanson, H. M., Witoslawski, J. J., Campbell, E. H., & Itkin, A. G. Estimation of relative antiavoidance activity of depressant drugs in squirrel monkeys. *Archives Internationales de Pharmacodynamie et de Therapie*, 1966, **161**, 7-16.

Kelleher, R. T. Chaining and conditional reinforcement. In W. K. Honig (Ed.), *Operant behavior: Areas of research and application*. New York: Appleton-Century-Crofts, 1966.

Kelleher, R. T., & Goldberg, S. R. Effects of naloxone on schedule-controlled behavior in monkeys. In E. Usdin, W. E. Bunney, Jr., & N. S. Kline (Eds.), *Endorphins in mental health research*. New York: Oxford University Press, 1979.

McMillan, D. E., Cole-Fullenwider, D. A., Hardwick, W. C., & Wenger, G. R. Phencyclidine discrimination in the pigeon using color tracking under second-order schedules. *Journal of the Experimental Analysis of Behavior*, 1982, **37**, 143-147.

Schuster, C. R., Dockens, W. S., & Woods, J. H. Behavioral variables affecting the development of amphetamine tolerance. *Psychopharmacologia*, 1966, **9**, 170-182.

Spealman, R. D., Kelleher, R. T., Morse, W. H., & Goldberg, S. R. Supersensitivity to the behavioral effects of opiate antagonists. *Psychopharmacology Bulletin*, 1981, **17**, 54-56.

Thompson, D. M. Repeated acquisition as a behavioral base line for studying drug effects. *Journal of Pharmacology and Experimental Therapeutics*, 1973, **184**, 506-514.

Thompson, D. M. Repeated acquisition of response sequences: Stimulus control and drugs. *Journal of the Experimental Analysis of Behavior*, 1975, **23**, 429-436.

Thompson, D. M., & Moerschbaecher, J. M. An experimental analysis of the effects of *d*-amphetamine and cocaine on the acquisition and performance of response chains in monkeys. *Journal of the Experimental Analysis of Behavior*, 1979, **32**, 433-444. (a)

Thompson, D. M., & Moerschbaecher, J. M. Drug effects on repeated acquisition. In T. Thompson & P. B. Dews (Eds.), *Advances in behavioral pharmacology* (Vol. 2). New York: Academic Press, 1979. (b)

Thompson, D. M., & Moerschbaecher, J. M. Effects of *d*-amphetamine and cocaine on strained ratio behavior in a repeated-acquisition task. *Journal of the Experimental Analysis of Behavior*, 1980, **33**, 141-148.

Thompson, D. M., & Moerschbaecher, J. M. Selective antagonism of the error-increasing effect of morphine by naloxone in a repeated-acquisition task. *Journal of the Experimental Analysis of Behavior*, 1981, **36**, 371-380.

Wenger, G. R. The effect of phencyclidine and ketamine on schedule-controlled behavior in the pigeon. *Journal of Pharmacology and Experimental Therapeutics*, 1976, **196**, 172-179.

Wenger, G. R. Cumulative dose-response curves in behavioral pharmacology. *Pharmacology, Biochemistry and Behavior*, 1980, **13**, 647-651.

Received April 19, 1982
Final acceptance August 24, 1982