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Acute Effects of Pentobarbital in a Monkey Operant Behavioral Test Battery

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FERGUSON, S. A. AND M. G. PAULE. *Acute effects of pentobarbital in a monkey operant behavioral test battery.* PHARMACOL BIOCHEM BEHAV 45(1) 107-116, 1993.—The effects of acute pentobarbital treatment were assessed using a complex operant test battery containing five tasks in which correct performance is thought to depend upon processes associated with short-term memory and attention [delayed-matching-to-sample (DMTS)], color and position discrimination [conditioned position responding (CPR)], motivation [progressive ratio (PR)], time perception [temporal response differentiation (TRD)], and learning [incremental repeated acquisition (IRA)]. Adult, male rhesus monkeys were tested 15 min after IV injection of saline or pentobarbital (1, 3, 5.6, 10, or 15 mg/kg). Behavioral endpoints measured included percent task completed, response rate or latency, and response accuracy. The order of task sensitivity to disruption by PBT was TRD > IRA = DMTS = PR > CPR, in which sensitivity was defined as a significant disruption in any aspect of task performance. PBT slowed response rates at 10.0 and/or 15.0 mg/kg in all tasks. Accuracy was decreased in the TRD task at ≥5.6 mg/kg but doses of ≥10.0 mg/kg were required to decrease accuracy in the IRA, DMTS, and CPR tasks. Thus, behavior thought to model time perception (TRD) was more sensitive than behavior modeling learning (IRA), short-term memory and attention (DMTS), and motivation (PR). CPR was the least sensitive behavior. Because pentobarbital exerts its effects at least in part via GABA systems, the effects in the current study were compared with those of a previous study of the acute effects of diazepam. The two compounds exerted fundamentally different effects on operant test battery performance.

Pentobarbital Monkey Operant behavior Learning Short-term memory Time perception Motivation Color and position discrimination

THE barbiturate pentobarbital (Nembutal) has been widely prescribed for the treatment of anxiety and insomnia; in addition, it has a high abuse liability. The National Household Survey on Drug Abuse found that 3.5% of people over 12 years of age reported one or more incidences of nonmedical use of sedatives, including barbiturates (14). Its medical use as a sedative has been largely replaced by the benzodiazepines (e.g., diazepam); however, it continues to be used as an acute treatment for convulsions and as an anesthetic in humans and animals (24). Similar to the benzodiazepines, pentobarbital appears to exert its behavioral effects by enhancing the inhibitory action of GABA in the CNS (8,16,25,34).

The psychopharmacology of acute pentobarbital administration has been widely investigated in pigeons and rats (1,7,9-11). In general, previous studies have assessed the effects of pentobarbital using classical operant behavior such as fixed-ratio or fixed-interval performance. Rarely have more "cognitive" functions such as time perception and complex learning been studied with respect to acute barbiturate treatment. Further, most studies have investigated the effects of pentobarbital using one or two behaviors rather than through the use of multiple behaviors in the same subjects. Such studies, particularly with nonhuman primates, are essential to provide a more comprehensive profile of the effects of acute pentobarbital administration.

To more completely describe the acute effects of pentobarbital treatment, the current study employed a monkey operant test battery (OTB) containing five behavioral tasks that are thought to model different CNS functions. The tasks and the CNS function that each is thought to model are: delayed-matching-to-sample (DMTS) (short-term memory and attention); conditioned position responding (CPR) (color and position discrimination); progressive ratio (PR) (motivation to work for food reinforcers); temporal response differentiation (TRD) (time perception); and incremental repeated acquisition (IRA) (learning). Studies in this laboratory have demonstrated that these tasks are differentially sensitive to the effects of a variety of psychotropic compounds (18).

Diazepam was one of the compounds previously investigated using the OTB (32). That study indicated that diazepam exerted its strongest effects on the OTB tasks thought to model time perception (TRD) and learning (IRA) and had little or no effects on color and position discrimination (CPR) or motivation (PR). Because in vitro studies have shown that

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diazepam and pentobarbital work through different mechanisms to enhance GABA transmission (33), it is important to compare the behavioral effects of pentobarbital with those of diazepam. Thus, the current study provides a profile of behavioral effects for acute pentobarbital administration as well as a comparison to that previously found for diazepam.

METHOD

Subjects

Eight adult, male rhesus monkeys (*Macaca mulatta*) between 5 and 9 years of age and weighing from 5–10 kg served as subjects. All monkeys had previously been trained under the schedules in the OTB for several years and had been used as subjects in previous studies on the acute effects of several psychoactive compounds (21,29–32). Animal housing, feeding, etc. were as previously described (29). Briefly, each monkey was individually housed and fed its daily allotment of food immediately after each test session. Water was available ad lib. Animal care and use procedures were in accordance with the American Association for Accreditation of Laboratory Animal Care (AAALAC) guidelines and approved by the Institutional Animal Care and Use Committee of the National Center for Toxicological Research.

Apparatus

The apparatus have been described in detail elsewhere (29) and consisted of portable primate restraint chairs, sound-attenuated behavioral chambers, operant panels, and computer consoles. The operant panels were equipped with three rear-projection press-plates, four retractable levers, six serial position indicator lights, and correct and incorrect response indicator lights. The press-plates, levers, and indicator lights were aligned horizontally, with the press-plates and serial position indicator lights located above the levers. Symbols and/or colors were projected onto the press-plates from the rear and, when pressed, each effected a switch closure. Serial position and correct and incorrect indicator lights were illuminated from behind the panel with various colors. A trough for reinforcer (190-mg banana-flavored food pellet) delivery was centered below the levers.

Operant Schedules

The use and description of the tasks contained in the OTB have been reported in detail elsewhere (17,29) and a diagram of the behavioral test panel is shown in Paule et al. (23). A brief description of each task follows.

PR. For the PR task, only the far-right retractable lever was extended. Each monkey was required to increase the number of lever presses required for each subsequent reinforcer. Initially, one or two lever presses (depending upon the individual monkey but the same for each subject every test day) resulted in reinforcer delivery. The number of responses required for the next reinforcer was increased by the initial number of lever presses required for the first reinforcer. Thus, if two lever presses were required for the initial reinforcer, four lever presses were required for the next, then six, eight, etc. The ratio increments were chosen so that marked periods of pausing or cessation of responding generally occurred during each baseline or vehicle PR component of the test session.

IRA. For the IRA task, all four retractable levers were extended and the serial position and correct and incorrect response indicator lights were used. Subjects were required to acquire, or learn, a new sequence of lever presses each test session. The IRA task began with the presentation of a one-lever response requirement (IRA1) and the rightmost serial position light on. Each response on the correct one of the four levers resulted in reinforcer delivery, and after 20 correct response sequences (criterion performance) a 1-min time-out period was followed by the presentation of an "incremented" two-lever response sequence (IRA2), in which a response on a different lever was required before a response on the original (IRA1) lever produced a reinforcer. After 20 errorless two-lever sequences (i.e., no errors were made between the first and last correct lever presses of the required sequence), the task was incremented to a three-lever sequence and so on, up to a six-lever sequence or until the allotted time elapsed. At the six-lever sequence, two levers were repeated in the sequence. The serial position indicator lights signaled position in the response sequence from left to right, indicating the remaining number of correct responses necessary for reinforcer delivery. Incorrect responses were followed by a 2-s time-out (incorrect response indicator light on) but did not reset the response requirement; thus, error correction was permitted. Correct responses were followed by illumination of the next rightmost serial position indicator light and the final correct response in a sequence was followed by a 1-s time-out, during which the correct response indicator light was illuminated.

CPR. For the CPR task, only the three press-plates were used (levers were retracted). At the start of each trial, the center press-plate was illuminated with either a solid red, yellow, blue, or green color (side press-plates were dark). Subjects continued the trial by making an "observing" response (a press) to the center plate, after which it was extinguished and the two side plates immediately illuminated white. If the center press-plate had been either blue or green, a response to the right press-plate (white) resulted in reinforcer delivery and initiation of a new trial. If the center press-plate had been either red or yellow, a response to the left press-plate (white) resulted in reinforcer delivery and initiation of a new trial. Responding to the incorrect position initiated a 10-s time-out period followed by the initiation of a new trial. The sequence of color presentation was random.

TRD. For the TRD task, only the far-left retractable lever was extended. Subjects were required to hold the lever in the depressed position for a minimum of 10 s but no longer than 14 s. Releasing the lever within this 4-s window resulted in reinforcer delivery. Releasing the lever too early or too late ended the ongoing trial, after which the monkey could immediately start another trial.

DMTS. For the DMTS task, only the three press-plate manipulanda were used (levers were retracted). At the start of each trial, one of seven white-on-black geometric symbols (the "sample") was projected onto the center press-plate in a random fashion (side press-plates were dark). To continue the trial, each monkey was required to make an "observing" response (a press) to the center plate. After the "observing" response was made, the center plate was extinguished for one of six time delays (i.e., 2, 4, 8, 16, 32, or 48 s, presented pseudorandomly) during which all three press-plates were dark. After the time delay, all three plates were illuminated, each with a different geometric symbol, only one of which matched the sample. A response to the "match" resulted in reinforcer delivery and initiation of a new trial with another sample stimulus (presented randomly). A nonmatching response was followed by a 10-s time-out period (all plates darkened) and then initiation of a new trial.

Behavioral Testing Procedure

Behavioral test sessions were conducted daily (Monday–Friday) and lasted approximately 50 min. Monkeys were rotated through nine identical behavioral test chambers so that, generally, no monkey was placed in the same chamber on 2 consecutive test days. Behavioral schedules alternated daily. For example, PR (10 min), IRA (35 min), and CPR (5 min) were presented on one test day; TRD (20 min) and DMTS (30 min) were presented the next test day.

Drug and Dosing Procedure

Pentobarbital (Sigma Chemical Co., St. Louis, MO) was dissolved in saline so that the final injection volume was 0.1 ml/kg and doses (1, 3, 5.6, 10, and 15 mg/kg, IV) were administered in a randomized order. Pentobarbital injections were given on Tuesdays and/or Fridays while vehicle injections were given on Tuesdays, Thursdays, and/or Fridays. Testing without prior injection was conducted on Mondays and Wednesdays. Due to the daily alternation of behavioral tasks, all pentobarbital doses were given twice to provide dose–response data for each operant task. Approximately 15 min after injection, each monkey was placed into an operant chamber and the behavioral session began 1 min later.

Behavioral Endpoints

The endpoints measured in each task have been described in detail elsewhere (29). Three fundamental measures were monitored for most tasks: percent task completed (PTC), response rate (RR) or latency, and response accuracy.

PTC. The PTC data are measures of a predetermined performance criteria and are functions of both RR and response accuracy. The PTC measure for each task is calculated by dividing the total number of reinforcers earned by the total number of reinforcers possible for that task and multiplying this quotient by 100. The total number of reinforcers possible was chosen arbitrarily based upon the length and difficulty of the task. The PTC endpoint is a convenient and comprehensive measure showing intra-animal stability and is useful for comparing drug effects on performance across tasks.

RR and latency. RR for each of the PR and TRD tasks were calculated by dividing the total number of lever presses by the total task time (in seconds). RR for each of the CPR, DMTS, and IRA tasks were calculated by dividing the total number of responses by the total task time minus time-out and any delay periods (in seconds). For the DMTS and CPR tasks, mean response latencies were also calculated for both observing and choice responses. In the DMTS and CPR tasks, if a monkey did not make an observing and/or choice response, a maximum response latency of 300 s was used in the analyses. In addition to overall RR for the IRA task (all response components considered), RR was measured for individual components or levels within the IRA task.

Response accuracy. Response accuracy for each of the CPR and DMTS tasks was calculated by dividing the number of correct responses by the total number of trials in a given session and multiplying this quotient by 100. Accuracy at each delay in the DMTS task was also measured. For the TRD and IRA tasks, response accuracy was calculated by dividing the total number of correct lever presses by the total number of lever presses in a given session and then multiplying this quotient by 100. As was done for IRA RR, response accuracy was measured within individual components or levels within the IRA task as well as for all components combined (overall accuracy). Response accuracy was not applicable for the PR task.

Other measures. For the TRD task, mean duration of lever hold and for the PR task the breakpoint (the magnitude of lever presses for the last ratio completed for which the monkey earned a reinforcer) were also measured. Within each sequence of the IRA task beyond IRA1, errors were measured as one of two types [similar to that of (22)]: a) Errors within sequences (recall errors) were defined as those incorrect lever presses occurring after "entry" into a response chain (i.e., after the first correct response of the chain) but before reinforcer delivery; and b) errors between sequences (acquisition errors) were defined as those errors occurring prior to the first correct response of a required sequence.

Statistical Analysis

Only those monkeys exhibiting stable performance for the measure of PTC after saline vehicle (control) injections were included in the statistical analyses. Stable performance was defined as that having a standard error of less than 15% of the mean for saline (control) sessions. During the current study, all eight monkeys exhibited stable vehicle baselines for the IRA and CPR tasks, seven for the PR task, and six for the TRD and DMTS tasks. For an animal's data to be included in the TRD and CPR accuracy analyses, a minimum of three trials must have been completed. For inclusion in the DMTS and IRA accuracy analyses, subjects must have completed a minimum of 10 trials. For each behavioral endpoint in each task, the overall effect of drug treatment on performance was determined using a one-way repeated-measures analysis of variance (ANOVA). If overall significance was evident ($p < 0.05$), then performance at each dose was compared to saline control performance using a Bonferroni correction (13).

RESULTS

Table 1 summarizes the results from the five OTB tasks. Control data (0.0 mg/kg) represent means for saline vehicle injection sessions. When compared to baseline (no injection) data, saline vehicle injections produced no statistically significant group effects on any of the endpoints examined. In Table 1, "overall" refers to combined data for all delays in the DMTS task and all levels in the IRA task.

PTC

Pentobarbital significantly decreased TRD PTC at doses ≥ 5.6 mg/kg while doses of ≥ 10 mg/kg decreased the DMTS, PR, and IRA PTC. CPR PTC was significantly decreased only at 15 mg/kg.

RR

Pentobarbital significantly decreased RR in all tasks except the CPR task at doses ≥ 10 mg/kg. At 15 mg/kg, RR in the CPR task was significantly decreased.

Accuracy

TRD accuracy was significantly decreased by ≥ 5.6 mg/kg and IRA accuracy was decreased at ≥ 10 mg/kg. DMTS and CPR accuracies were significantly decreased only at the highest dose of 15 mg/kg.

Response Latencies

Observing and choice response latencies in the CPR task were equisensitive to pentobarbital and significantly increased

TABLE 1

Task	Dose of Pentobarbital (mg/kg)					
	0.0	1.0	3.0	5.6	10.0	15.0
Delayed matching to sample (n = 6)						
Overall % task completed	40.76 ± 5.51	44.16 ± 6.61	42.22 ± 6.32	34.50 ± 10.59	23.06 ± 3.33*	4.44 ± 0.00*
Overall response rate (resp/s)	0.59 ± 0.13	0.66 ± 0.12	0.58 ± 0.14	0.57 ± 0.17	0.24 ± 0.07*	0.04 ± 0.03*
Observing response latencies (s)	3.49 ± 0.72	2.07 ± 0.39	2.92 ± 0.87	12.75 ± 10.96	25.25 ± 18.28	216.19 ± 7.25*
Choice response latencies (s)	2.04 ± 0.50	1.44 ± 0.15	2.05 ± 0.63	1.90 ± 0.61	11.78 ± 9.68	3.97 ± 0.87
Accuracy	70.71 ± 5.63	70.56 ± 4.67	69.86 ± 7.87	62.68 ± 7.03	61.85 ± 8.30	57.12 ± 0.00*
Conditioned position responding (n = 8)						
Percent task completed	94.20 ± 1.74	100.00 ± 0.00	100.00 ± 0.00	100.00 ± 0.00	93.75 ± 4.89	32.50 ± 8.83*
Response rate (resp/s)	1.20 ± 0.12	1.42 ± 0.15	1.31 ± 0.16	1.22 ± 0.13	0.94 ± 0.09	0.32 ± 0.09*
Observing response latencies (s)	2.60 ± 0.47	1.28 ± 0.19	1.45 ± 0.24	1.52 ± 0.23	2.03 ± 0.37	79.56 ± 48.13*
Choice response latencies (s)	0.28 ± 0.03	0.25 ± 0.03	0.26 ± 0.03	0.28 ± 0.03	0.34 ± 0.04	1.07 ± 0.46*
Accuracy	95.10 ± 1.06	98.78 ± 0.51	96.31 ± 1.23	95.88 ± 0.96	92.58 ± 1.59	76.70 ± 2.42*
Progressive ratio (n = 7)						
Percent task Completed	18.43 ± 1.43	18.33 ± 1.76	16.07 ± 1.60	19.76 ± 3.72	11.11 ± 3.41*	1.79 ± 0.76*
Response rate (resp/s)	2.31 ± 0.35	2.19 ± 0.41	1.81 ± 0.34	1.61 ± 0.37	1.00 ± 0.30*	0.07 ± 0.05*
Breakpoint	105.87 ± 12.63	103.17 ± 13.60	93.00 ± 12.30	86.00 ± 14.24	58.00 ± 14.26*	11.00 ± 5.50*
Temporal response differentiation (n = 6)						
Percent task completed	32.72 ± 3.91	27.36 ± 7.97	29.44 ± 4.43	16.53 ± 6.22*	0.00 ± 0.00*	0.00 ± 0.00*
Response rate (resp/s)	0.14 ± 0.02	0.11 ± 0.02	0.15 ± 0.03	0.15 ± 0.03	0.06 ± 0.02*	0.03 ± 0.01*
Accuracy	28.61 ± 5.53	27.59 ± 7.82	22.44 ± 4.51	8.96 ± 3.46*	0.00 ± 0.00*	0.00 ± 0.00*
Duration of lever hold (seconds)	5.96 ± 0.84	6.88 ± 0.85	5.76 ± 0.82	2.81 ± 0.68*	1.03 ± 0.15*	1.08 ± 0.30*
Incremental repeated acquisition (n = 8)						
Overall % task completed	65.75 ± 6.59	73.65 ± 7.61	64.38 ± 8.05	60.63 ± 9.05	46.88 ± 7.16*	18.02 ± 1.95*
Overall response rate (resp/s)	1.24 ± 0.18	1.48 ± 0.26	1.15 ± 0.24	0.90 ± 0.19	0.72 ± 0.14*	0.16 ± 0.04*
Overall accuracy	60.87 ± 4.66	63.41 ± 5.16	56.25 ± 6.36	54.36 ± 6.48	44.27 ± 5.99*	25.14 ± 4.14*

*Significant differences from saline controls as determined by Fisher's (LSD) t-test ($p < 0.05$).

at 15 mg/kg. Observing response latency in the DMTS task was increased at 15 mg/kg; however, choice response latency was not significantly affected by any dose. Because a latency of 300 s was assigned to subjects not responding (and there were several subjects that did not respond after 15 mg/kg), the mean observing response latencies and standard errors for both tasks were significantly increased at this dose.

PR Breakpoint

Breakpoint (the number of lever presses made for the last reinforcer) was significantly decreased at 10 and 15 mg/kg.

Duration of TRD Lever Hold

Mean duration of lever hold was decreased by pentobarbital at ≥5.6 mg/kg. Figures 1 and 2 show the effects of pentobarbital on the frequency of lever holds that were less than 2 s in duration and those that were more than 2 s in duration. Lever holds less than 2 s (i.e., response bursts) are frequent in the TRD task and are best represented separately from those greater than 2 s.

IRA Sequence Progression

Performance of the initial one-lever response component (IRA1) to criterion represents 16.7% task completed. Completion of the two- and three-lever sequence components (IRA2 and IRA3) represents 33 and 50% task completed, respectively. Table 2 indicates the number of monkeys that completed various IRA components and their accuracy and RR for each component. In general, low doses of pentobarbital did not significantly interfere with the completion of IRA1 or IRA2, and five monkeys were able to complete IRA4.

IRA Errors

Figures 3 and 4 indicate the effects of pentobarbital on between- and within-sequence errors, respectively, in the IRA task at the two-lever sequence (IRA2).

DISCUSSION

The order of OTB task sensitivity to disruption by pentobarbital was TRD > IRA = DMTS = PR > CPR. As defined in previous studies, "sensitivity" refers to a significant alteration in any of the three major aspects of task performance (PTC, overall RR, and accuracy or breakpoint) at doses lower than those affecting performance of the other tasks. Thus, behavior thought to model time perception (TRD) was more sensitive than behavior modeling learning (IRA), short-term memory and attention (DMTS), and motivation (PR). Color and position discrimination (CPR) was the least sensitive behavior. The order of OTB task sensitivity for pentobarbital differs from those of chlorpromazine, atropine, physostigmine, phencyclidine, MK-801, *d*-amphetamine, morphine, Δ-9-tetrahydrocannabinol, marijuana smoke, and diazepam (2,18–21,28–32), further demonstrating that the OTB tasks are preferentially sensitive to compounds from different drug classes. In addition, the findings from the current study are consistent with those of previous studies of acute pentobarbital administration and extend the profile of pentobarbital effects on complex cognitive behaviors. Finally, the effects of pentobarbital on OTB performance differed from those of diazepam (32), particularly with respect to TRD endpoints. Thus, while the two compounds may have GABAergic similarities, their behavioral effects likely do not derive from such similarities.

If restricted to the PTC endpoint, the order of OTB task sensitivity remained as noted above; however, if only overall RR is considered, there is a somewhat different order. With the exception of CPR RR, overall RRs in the remaining four tasks were equally sensitive to disruption by pentobarbital. This similar sensitivity may indicate that the decrease in RR was due to sedative effects of pentobarbital, even though such effects might be expected to be present at the same dose in the CPR task. However, CPR endpoints have traditionally been less sensitive to disruption than those of other tasks [one exception was acute atropine administration; see (21)]. Baseline

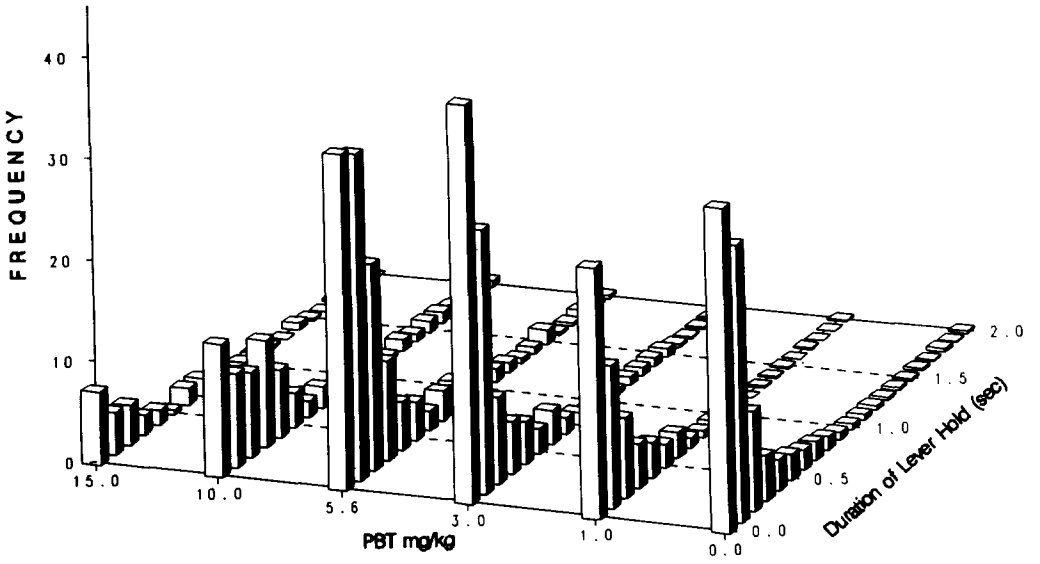

FIG. 1. Effect of pentobarbital on mean duration of lever hold in the temporal response differentiation (TRD) task for holds less than 2 s in duration. Each sond is divided into 0.1-s intervals (i.e., the first bar represents the frequency of lever holds with a duration of 0.01–0.09 s).

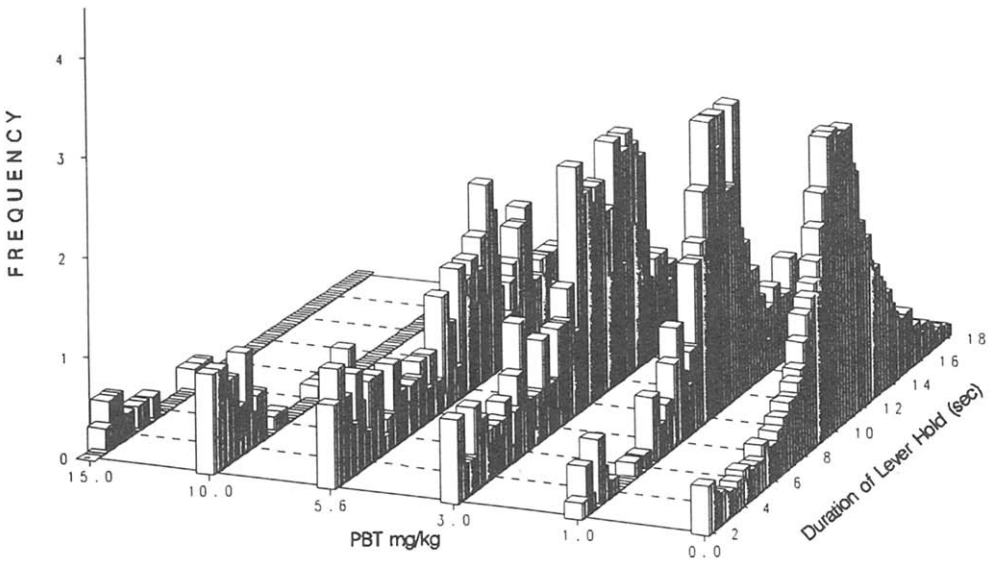

FIG. 2. Effect of pentobarbital on mean duration of lever hold in the temporal response differentiation (TRD) task for holds more than 2 s in duration. Each second is divided into 0.2-s intervals (i.e., the first bar represents the frequency of lever holds with a duration of 2.01–2.19 s).

RR did not appear to predict sensitivity to disruption because IRA and CPR RR were nearly identical under saline conditions.

Several studies have reported that acute pentobarbital administration produces a nonmonotonic effect on RR in many operant paradigms: low doses increase and high doses decrease RR. Such effects have been described using fixed-interval schedules (1,12,26), learning tasks (22), and matching-to-sample tasks (35,36). In the current study, there were indications of similar rate increases at low doses, particularly for the DMTS, CPR, and IRA tasks, in which 1 mg/kg increased RR; however, these increases did not reach statistical significance. At higher doses of pentobarbital, RR decreased as has been previously observed.

Prior drug exposure has been reported to interfere with pentobarbital-induced RR increases; specifically, Glowa and Barrett (4) reported that in monkeys administration of morphine within 1 week of subsequent pentobarbital treatment prevented the RR increase typically associated with pentobarbital administration. Monkeys in the current study were also treated acutely with morphine as part of a prior study (30). However, prior exposure to morphine seems an unlikely explanation for the failure to observe a significant RR increase at low doses of pentobarbital because a minimum of 3 months had elapsed between the last morphine treatment and the first pentobarbital treatment. Additionally, acute administration of morphine in rats prior to pentobarbital administration did not prevent significant pentobarbital-induced increases in RR in an IRA task (22).

For the DMTS and CPR tasks, there were two additional measures of rate: latencies to make observing and choice responses. Observing response latencies in both tasks were unaffected by pentobarbital at doses ≤ 10 mg/kg. Even at the highest dose, observing response latencies in both tasks were relatively unaffected for those monkeys that emitted observing responses. Thus, initiation of trials (i.e., emitting an observing response) was relatively insensitive to pentobarbital. Similarly, in the DMTS task, the completion of a trial, signaled by a choice response, was not significantly altered by pentobarbital. In the CPR task, however, choice response latency was more sensitive to pentobarbital than either CPR observing response latency or choice response latency in the DMTS task. CPR choice response latency was nearly doubled for those monkeys that responded after the highest dose. Thus, while CPR endpoints have generally not been as sensitive to disruption by drugs as have endpoints in the other tasks, choice response latency was more sensitive here than was its DMTS counterpart.

The order of OTB task sensitivity to pentobarbital more clearly differentiated between tasks if compared solely with respect to accuracy: TRD > IRA > DMTS = CPR (the PR task does not have an accuracy measure). Accuracy in the TRD task was by far the most sensitive OTB measure, decreasing to approximately 30% of control values at 5.6 mg/kg, while IRA, DMTS, and CPR accuracies were significantly decreased to 70–80% of control values only at higher doses. In general, the TRD task appears to be the most "difficult" of the OTB tasks because baseline accuracy is low relative to that for DMTS, IRA, and CPR. Further, it is generally the most sensitive OTB task to disruption by psychotropic compounds (2,20,29,32).

Performance in the TRD task is thought to depend upon the function of time perception and accuracy is directly related to duration of lever hold. In humans, time perception has been shown to be significantly affected by barbiturates (5). Subjects were instructed to indicate whether the amount of time between two tones was less or more than 1 s. Those subjects treated with secobarbital underestimated the length of 1 s, a finding consistent with the subjective effect of "time flying." Those results are intriguing in light of the TRD results in the current study because it could be postulated that a similar pentobarbital-induced "time flying" effect was apparent. The mean duration of lever hold decreased from 6 s under control conditions to less than 3 s at 5.6 mg/kg pentobarbital,

TABLE 2

	Dose of Pentobarbital (mg/kg)					
	0.0	1.0	3.0	5.6	10.0	15.0
IRA one-lever sequence (IRA1)						
Animals completing	8/8	8/8	8/8	8/8	8/8	5/8
Response rate (resp/s)	1.55 ± 0.18	1.57 ± 0.23	1.32 ± 0.19	1.27 ± 0.24	0.79 ± 0.08*	0.20 ± 0.02*
Accuracy	57.22 ± 4.94	72.91 ± 6.67	59.24 ± 10.19	51.94 ± 5.30	48.05 ± 9.42	32.44 ± 5.18*
IRA two-lever sequence (IRA2)						
Animals completing	8/8	8/8	8/8	7/8	6/8	0/8
Response rate (resp/s)	1.54 ± 0.09	1.65 ± 0.17	1.41 ± 0.14	1.08 ± 0.20*	0.87 ± 0.17*	0.22 ± 0.06*
Accuracy	62.90 ± 5.05	66.78 ± 7.08	63.26 ± 5.54	63.48 ± 5.93	52.04 ± 6.17*	†
Between-sequence errors	31.26 ± 8.19	26.25 ± 10.55	29.63 ± 10.42	39.29 ± 19.68	42.33 ± 8.05	†
Within-sequence errors	17.64 ± 4.29	8.12 ± 3.00	13.00 ± 6.84	19.57 ± 7.19	25.00 ± 9.63	†
IRA three-lever sequence (IRA3)						
Animals completing	8/8	8/8	7/8	6/8	4/8	0/8
Response rate (resp/s)	1.51 ± 0.19	1.71 ± 0.22	1.27 ± 0.25	1.28 ± 0.19	1.01 ± 0.24*	†
Accuracy	66.63 ± 3.69	73.80 ± 3.86	64.97 ± 6.53	61.25 ± 6.99	55.95 ± 6.55*	†
Between-sequence errors	37.33 ± 6.74	25.00 ± 12.66	39.67 ± 18.78	54.00 ± 20.54	80.50 ± 31.92*	†
Within-sequence errors	36.65 ± 8.03	19.00 ± 8.98	49.33 ± 18.99	30.83 ± 9.24	51.75 ± 21.97	†
IRA four-lever sequence (IRA4)						
Animals completing	7/8	6/8	5/8	3/8	1/8	0/8
Response rate (resp/s)	1.47 ± 0.21	1.82 ± 0.31	1.69 ± 0.19	1.30 ± 0.20	0.83 ± 0.13*	†
Accuracy	71.93 ± 3.64	70.26 ± 3.35	69.91 ± 6.52	77.19 ± 7.32	69.96 ± 0.00	†
Between-sequence errors	37.31 ± 7.82	32.33 ± 7.91	39.20 ± 17.23	17.67 ± 7.26	21.00 ± 0.00	†
Within-sequence errors	30.34 ± 7.00	23.33 ± 4.21	46.40 ± 14.17	32.67 ± 23.67	46.00 ± 0.00	†
IRA five-lever sequence (IRA5)						
Animals completing	6/8	2/8	2/8	2/8	0/8	0/8
Response rate (resp/s)	1.47 ± 0.21	1.78 ± 0.30	1.35 ± 0.30	1.39 ± 0.04	0.65 ± 0.00	†
Accuracy	75.76 ± 3.54	80.64 ± 9.25	89.87 ± 2.04	85.56 ± 6.75	†	†
Between-sequence errors	32.92 ± 7.54	32.33 ± 28.39	6.50 ± 5.50	12.50 ± 8.50	†	†
Within-sequence errors	20.25 ± 3.69	20.00 ± 9.02	8.00 ± 2.00	12.00 ± 6.00	†	†

*Significant differences from saline controls as determined by Fisher's (LSD) t-test ($p < 0.05$).
†Only measured if level is completed by one or more animals.

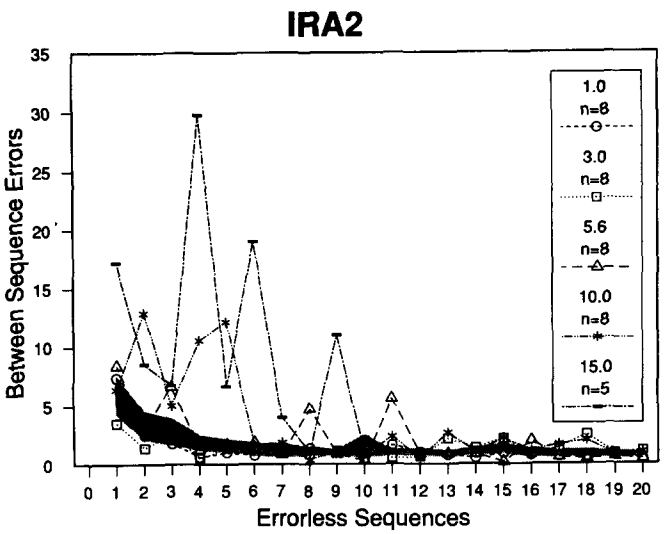

FIG. 3. Effect of pentobarbital on between-sequence errors in the incremental repeated acquisition (IRA) task at the two-lever response component (IRA2). The shaded area represents the 95% confidence interval constructed from vehicle control sessions.

indicating underestimation of the necessary duration of lever hold. At higher doses, lever hold duration continued to decrease.

IRA task accuracy was not as sensitive to pentobarbital as was TRD task accuracy. Although not statistically significant, low doses of pentobarbital appeared to increase accuracy, particularly evident at IRA5 (see Table 2). A similar effect was observed in rats in which a low dose of pentobarbital (1 mg/kg) increased accuracy at IRA2 (22). In the current study, higher doses slowed response rates such that most monkeys never progressed to higher IRA components.

Accuracies in the DMTS and CPR tasks were much less sensitive to the effects of pentobarbital than was accuracy in the other tasks. Other studies have also reported that DMTS accuracy in monkeys is relatively insensitive to pentobarbital (3,15). In addition, the magnitude of the maximum decrement caused by the highest dose of pentobarbital was much less than that for other endpoints within the DMTS and CPR tasks.

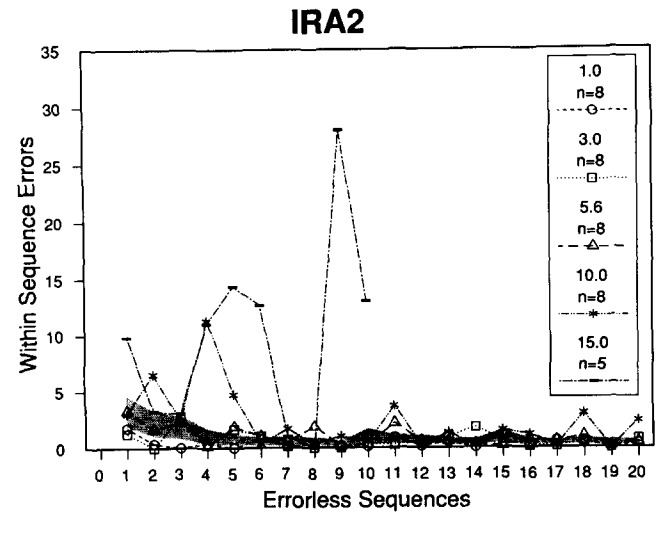

FIG. 4. Effect of pentobarbital on within-sequence errors in the incremental repeated acquisition (IRA) task at the two-lever response component (IRA2). The shaded area represents the 95% confidence interval constructed from vehicle control sessions.

It is possible to compare and contrast the effects of acute pentobarbital and diazepam administration on OTB performance. Although not every endpoint described here was reported for acute diazepam treatment (32), there were still sufficient data available to distinguish between the two compounds on the five OTB tasks. For example, overall RR for the PR, TRD, and IRA tasks were distinctive for pentobarbital and diazepam administration. Diazepam decreased response rate in the IRA task at doses that did not significantly alter PR or TRD response rates (32), whereas IRA, PR, and TRD response rates were equisensitive to pentobarbital.

Diazepam, like pentobarbital, produced no statistically significant effects on observing response latencies in the DMTS or CPR tasks (32). Acute diazepam administration increased observing response latency in some monkeys, leading to increased group variability in that measure, whereas pentobarbital abolished observing responses in some monkeys, resulting in a similar effect. Choice response latencies in the DMTS and CPR tasks were not reported in the diazepam study and thus a comparison with pentobarbital is not possible at this time.

TRD accuracy proved to be the most sensitive overall OTB measure in the current study and in the previous diazepam study (32). However, the drug-induced accuracy decrements were associated with entirely different response patterns. The TRD accuracy decrease at 5.6 mg/kg pentobarbital was associated with a decrease in the average duration of lever hold. Neither overall number of responses nor RR were significantly altered at this dose. Thus, monkeys responded as frequently as under control conditions but released the lever too early. The diazepam-induced decrement was associated with an increase in lever holds of less than 1 s in duration that resulted in reduced accuracy. Thus, drug effects on lever hold duration were particularly distinct for the two compounds.

Acute diazepam administration resulted in accuracy decrements in the IRA task with no indication of a facilitative effect at any dose (32). Similar to pentobarbital, between- and within-sequence errors in the two-lever sequence (IRA2) were not differentially affected by diazepam (unpublished data).

In the current study, DMTS and CPR accuracies were equally insensitive to pentobarbital whereas DMTS, but not CPR, accuracy was differentially decreased by diazepam (32). Pentobarbital did not preferentially alter DMTS accuracy at any specific delay interval and there was no dose that decreased accuracy at all delays. Conversely, diazepam at 2 mg/kg decreased DMTS accuracy at all delays.

Because both pentobarbital and diazepam are GABAergic compounds, previous studies have specifically contrasted their behavioral effects. In humans, diazepam administration has been reported to decrease social interactions and increase hostility ratings whereas pentobarbital administration had no such effects (6). Where behavioral similarities do exist between pentobarbital and diazepam, administration of certain pharmacological compounds can reveal subtle differences. For example, Risner and Shannon (26) reported that pentobarbital and diazepam produced similar effects on performance in fixed-interval and fixed-ratio schedules. However, the behavioral effects of diazepam were antagonized by CGS 8216, a benzodiazepine antagonist, while those produced by pentobar-

bital were not. Pentobarbital and diazepam administration resulted in similar effects in rats trained to make a choice response in the presence or absence of brain stimulation (27). The partial inverse benzodiazepine agonist RO 15-4513 reversed the effects of diazepam but not those of pentobarbital.

The differences produced by such compounds may be related to the differences they produce on chloride channel kinetics. Diazepam has been reported to increase and pentobarbital to decrease the frequency of channel openings and pentobarbital increased average open-channel lifetime while diazepam had few effects (33).

In summary, acute pentobarbital treatment in rhesus monkeys produced a unique profile of effects in operant tasks thought to depend upon brain functions associated with time perception, learning, short-term memory and attention, motivation, and color and position discrimination (TRD > IRA = DMTS = PR > CPR). This profile was significantly different from that noted after diazepam administration and the two compounds were easily differentiated based upon their effects on duration of lever hold and response rate in the time perception task and accuracy in the short-term memory and attention task. Multiple comparisons of the acute effects of drugs on several behaviors within the same subjects, available only when using instruments such as the OTB, allow assessment of drug sensitivities across and within different tasks that are thought to represent different brain functions and thus, allow a relatively comprehensive description of their behavioral effects.

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