PENTOBARBITAL SELF-ADMINISTRATION IN RHESUS MONKEYS: DRUG CONCENTRATION AND FIXED-RATIO SIZE INTERACTIONS

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Performances of three rhesus monkeys were reinforced by the oral delivery of pentobarbital and studied as functions of fixed-ratio size and drug concentration. Pentobarbital solutions and water were concurrently available on identical reinforcement schedules from separate liquid-delivery systems during 3-hour sessions. Under a fixed-ratio 16 schedule of drug availability, a descending series of drug concentrations was tested (4, 2, 1, 0.5, 0.25, 0.125, and 0.0625 mg/ml, followed by a retest at 4 mg/ml). Partial concentration series beginning with the highest concentration were repeated with fixed-ratios of 32 and 64, with a fixed-ratio 128 for two monkeys, and with fixed-ratio 256 for one. At each fixed-ratio value, response rate and number of drug deliveries were inverted U-shaped functions of pentobarbital concentration. Drug intake (mg/kg/session) increased directly with drug concentration. As the fixed-ratio size was increased, the number of liquid deliveries decreased. For each drug concentration, when the numbers of drug deliveries at fixed-ratios of 32, 64, and 128 responses were plotted as percentages of those obtained at fixed-ratio 16, the following orderly relationship emerged: the higher the drug concentration, the less that drug deliveries were decreased by increases in fixed-ratio size. This relationship indicates an increase in reinforcing efficacy with increases in pentobarbital concentration.

Key words: pentobarbital self-administration, pentobarbital concentration, oral route, fixed-ratio schedules, concurrent schedules, relative reinforcing efficacy, rhesus monkeys

A consistent finding in drug self-administration studies is an inverted U-shaped function between number of drug deliveries and the size of the drug dose or concentration (Schuster & Johanson, 1974; Spealman & Goldberg, 1978): As drug dose or concentration is increased, the number of drug deliveries first increases and then

decreases. In most of these studies only a single schedule value was employed. One purpose of the present study was to determine the relationship between pentobarbital concentration and number of drug deliveries over a range of pentobarbital concentrations and fixed-ratio (FR) values.

A second objective was to evaluate the relative reinforcing efficacy of different pentobarbital concentrations. The quantitative relations present between different reinforcer magnitudes (mg of orally delivered pentobarbital) and amount of behavior emitted, relative to baseline, were examined. A particular point of interest was to determine whether higher concentrations of pentobarbital would maintain more behavior, relatively, than lower concentrations, as the size of the fixed-ratio schedule was increased.

The relative reinforcing efficacy of drugs has been studied with two procedures: progressive-ratio schedules and concurrent schedules. Griffiths, Brady, and Snell (1978) substituted diethylpropion, chlorphentermine, or fenfluramine for the cocaine that

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was being self-administered intravenously by baboons. They then compared the "breaking point" of progressive-ratio performance for each drug, and ranked the relative ability of these drugs to maintain responding. The procedure yielded an ordinal ranking, from highest to lowest, of cocaine, diethylpropion, chlorphentermine, and fenfluramine.

Other researchers investigating drug reinforcers have used concurrent schedules. Johanson and Schuster (1975) assessed drug preference and compared response rates of monkeys intravenously self-infusing cocaine or methylphenidate. Concurrent FR 5 schedules were used, with the first response on one schedule precluding reinforcement on the other schedule. A 15-min timeout period was scheduled after each drug delivery to avoid rate-disruptive drug effects. Response rates were compared between drug and saline, and between different doses of the same drug (0.05 to 1.5 mg/kg/infusion cocaine; 0.075 to 0.7 mg/kg/infusion methylphenidate). Drug was always preferred to saline, and cocaine maintained more responding than did methylphenidate. For methylphenidate, higher doses were preferred to lower ones; this was true up through 0.5 mg/kg/infusion for cocaine. With monkeys self-administering cocaine intravenously, Iglauer and Woods (1974) arranged drug delivery according to concurrent variable-interval (VI) 1-min schedules. A constant dose (0.05 or 0.1 mg/kg/infusion) was available on one schedule and a variable dose (0.013 to 0.8 mg/kg/infusion) was available on the other. Higher or lower response rates occurred on the variable-dose schedule, depending on whether the variable dose was greater or less, respectively, than the constant dose. A graded ordering of response rates according to dose size was not obtained on the variable-dose schedule, however, as exclusive schedule preferences developed within conditions.

In the present study, water, the drug vehicle, was concurrently available with pentobarbital solutions (water plus pentobar-

bital) under identical FR schedules. In a systematic sequence, pentobarbital solutions of different concentration were presented. Thus responding maintained by the drug solution and by its vehicle was compared within sessions, and different magnitudes (concentrations) of a single reinforcer, pentobarbital, were compared across sessions.

Pentobarbital is a short-acting barbiturate that is abused by humans (Jaffe, 1980) and functions as a reinforcer when taken orally (Griffiths, Bigelow, & Liebson, 1979; Pickens, Cunningham, Heston, Eckert, & Gustafson, 1977). Pentobarbital can also serve as a reinforcer for rhesus monkeys when it is delivered intravenously (Goldberg, Hoffmeister, Schlichting, & Wuttke, 1971; Johanson, 1982; Winger, Stitzer, & Woods, 1975), intragastrically (Altshuler, Weaver, & Phillips, 1975; Yanagita & Takahashi, 1973), or orally (DeNoble, Svikis, & Meisch, 1982; Kliner & Meisch, 1982; Meisch, Kliner, & Henningfield, 1981).

METHOD

Subjects

Three male rhesus monkeys, M-G2, M-B, and M-LA, served. They were maintained at reduced weights during the experiment. Their free-feeding weights were 12.4, 10.4, and 15.5 kg, respectively; during the experiment they were maintained at 79, 88, and 66 percent of those weights, respectively. Monkey M-LA was the heaviest and was also slightly obese when freely fed; his feeding ration during the experiment maintained a healthy-looking body condition similar to that of the other two animals. The monkeys were food deprived because previous research indicated that high rates of responding are maintained by the oral delivery of pentobarbital when monkeys are food deprived but not when they are food satiated (Kliner & Meisch, 1982).

Monkey M-G2 had participated in an earlier study on the establishment of orally delivered pentobarbital as a reinforcer (DeNoble et al., 1982), and for this subject

the drug was serving as a reinforcer. Subject M-B had previously been exposed to oral self-administration of the drugs etonitazene and phencyclidine. Monkey M-LA was experimentally naive. For the latter two monkeys, increasing concentrations of pentobarbital were gradually added to the water available under an FR 1 schedule during sessions. Within these acquisition sessions, the only liquid available was the pentobarbital solution, with side position alternating daily. Fixed-ratio size was then systematically increased. Following this procedure, all three subjects reliably self-administered pentobarbital solutions in greater quantities than the vehicle, water, when these were scheduled concurrently.

Apparatus

The three monkeys were permanently housed in stainless-steel cages (Hoeltge, No. HB-108) measuring 77 by 76 by 100 cm. The fronts of the cages were barred. In one of the side walls, holes admitted stimulus lights and two brass drinking spouts that were attached to a steel-plate work panel that fastened to the outside of the cage. The two brass drinking spouts (1.2 cm outside diameter, 0.2 cm inside diameter) protruded 2 cm into the cage. These were located 52 cm above the floor and symmetrically 15.5 cm either side of the work panel midline. Located 12 cm above each spout was a 2.8-W stimulus light. Each light had a translucent green jewel cover. Both lights were on throughout the session, either constantly illuminated, on the side where water was available, or blinking at a rate of 10 Hz, on the side where pentobarbital was available. When water was accessible between sessions, the water-side light was steadily on. Two pairs of feedback stimulus lights were located behind a Plexiglas plate that surrounded each spout. Each pair consisted of two 1.1-W stimulus lights that were placed at the corners of an "X" pattern around each spout; each light was 3 cm from the spout. Translucent lens covers were green for one pair, white for the other. Each light within a pair was 180 degrees from the other.

During the timeout (TO) periods, none of the equipment was operational. When TO was not in effect, a lip contact (designated as the operant response) with an appropriate spout activated a drinkometer circuit and resulted in the illumination of one of the two pairs of translucent feedback stimulus lights. When pentobarbital was the available liquid (within sessions only), responses activated the green pair of lights. Similarly, when water was the available liquid (both within and between sessions), responses activated the white pair of lights. The lights remained illuminated as long as the monkey maintained lip contact.

Outside the cage, attached to the back of the brass spouts, were solenoid-operated valves controlling liquid flow. Liquids were contained in covered stainless-steel reservoirs that were connected via polyethylene tubing to the valves. Each reinforced response (both within and between sessions) operated the solenoid for a maximum of 150 ms, allowing delivery of approximately 0.64 ml of liquid. A break in lip contact during liquid delivery terminated solenoid operation, thus preventing spillage. The drinking device and work panel are more fully described elsewhere (Henningfield & Meisch, 1976; Meisch, Henningfield, & Thompson, 1975). Cumulative recorders and solid-state programming and recording equipment were located in an adjacent room.

Procedure

The monkeys lived in the experimental chambers. Sessions were 3 hr in length and were conducted daily, 7 days a week. Prior to the session there was a 1-hr TO, during which water consumption values for the intersession period were recorded and solutions for the session were placed in the reservoirs. A second 1-hr TO after the session allowed recording of data from the session and placement of water in one of the reservoirs, where it was available under an FR 1 schedule during the intersession period. After the 1-hr postsession TO, intersession access to water occurred for 1 hr,

followed by another 1-hr TO, during which the monkeys received their daily ration of Purina Monkey Chow. This TO was followed by continued intersession access to water for the remaining 17 hr of the day.

The monkeys were first tested at FR 16. Lower fixed ratios were not tested in order to prevent possible death from drug overdose. Drug and water solutions were concurrently available, with their positions reversed daily. Each series of drug concentrations began at 4 mg/ml. Each concentration was presented until 10 sessions of stable behavior were obtained. Stability was defined as no observed increasing or decreasing trend in the number of liquid deliveries over the 10-day period. The number of sessions required to reach stability ranged from 10 to 46, but was usually less than 20. After stability was achieved in a condition, the drug concentration was decreased by half. Halving of the concentration continued across conditions until the mean number of liquid deliveries stopped increasing and began to decrease. After testing at the lowest concentration reached by this procedure, the monkeys were retested at 4 mg/ml. Interpolated between testing at the lowest concentration and the retest at 4 mg/ml, the monkeys were given the intervening concentrations, in an ascending order, for two sessions each. This series of increasing concentrations was presented in order to avoid possible disruption from abrupt taste changes accompanying a switch from a low concentration to 4 mg/ml.

After the retest at 4 mg/ml, the FR was doubled in size and another concentration series commenced. Each monkey was tested under these conditions until the following two conditions occurred: an FR value was reached at which data from fewer than three concentrations in a series were obtained, and the mean number of drug deliveries at the lowest concentration in that series was less than 25% of its FR 16 baseline.

Drug

Stock solutions (6.25 mg/ml), prepared weekly from sodium pentobarbital and tap water, were stored at 3° C. Daily prepara-

tion of solutions for the sessions was accomplished by dilution of the stock solution with tap water approximately 2 hr prior to the session. Concentrations are expressed as the salt.

RESULTS

Figure 1 shows that at each FR value, the rate of responding was an inverted U-shaped

Fig. 1. Mean response rate as a function of pentobarbital concentration and fixed-ratio size. Abscissa: pentobarbital concentration, log scale; ordinate: mean responses per second over the 3-hr session at each condition. Circles represent values for pentobarbital. Triangles represent values for the concurrently available water. Unconnected points at the 4.0 mg/ml concentration are retest values. Points are means of the last 10 stable sessions under each condition. Brackets indicate the S.E.M. Absence of brackets at a point indicates that the S.E.M. fell within the area occupied by the plotted point. Note that Monkey M-LA was not tested at FRs 128 and 256 and that Monkey M-B was not tested at FR 256.

function of pentobarbital concentration. As FR size increased, the concentration that maintained the highest rate of responding tended to shift to higher values.

Figure 2 shows representative cumulative records for Monkey M-G2 at each FR value for the 1 mg/ml concentration. The overall time course of responding during each session was characterized by a high rate at the beginning of the session, followed by extended pauses that were interrupted by one or more subsequent bouts of responding. These later bouts were usually of shorter duration than the initial bout. Responding, when it occurred, was characterized by a high running rate, with occasional postreinforcement pauses.

Figure 3 illustrates that at each FR size, drug deliveries were an inverted U-shaped function of concentration. At all concentra-

tions, numbers of drug deliveries decreased as FR size increased. Generally, water deliveries were substantially less in number than drug deliveries. Retest values at the 4 mg/ml concentration approximated initial values throughout. For Monkey M-B, at fixed-ratios of 16 and 32 the mean number of water deliveries exceeded the mean number of 4 mg/ml pentobarbital deliveries. However, further increases in FR size resulted in relatively greater decreases in water than drug deliveries, and 4 mg/ml drug deliveries came to exceed water deliveries.

In Figure 4, for each drug concentration the number of liquid deliveries obtained at FRs greater than 16 is plotted as a percentage of the number obtained at FR 16. This type of plot permits a comparison across concentrations of the relative change in the number of deliveries as the FR size is in-

Fig. 2. Representative cumulative records for Monkey M-G2 showing performance under various FR sizes at the 1.0 mg/ml concentration. Abscissa: time; ordinate: cumulative lip-contact responses. Diagonal marks of the response pen show drug deliveries after completion of each FR. Each record shows a complete 3-hr session. The pen reset after every 400 responses. Deliveries of water are shown by slash marks on the straight line below each cumulative record.

Fig. 3. Mean number of liquid deliveries as a function of pentobarbital concentration and fixed-ratio size. Abscissa: pentobarbital concentration, log scale; ordinate: mean liquid deliveries during the 3-hr session. Circles represent values for pentobarbital. Triangles represent values for the concurrently available water. Unconnected points at the 4.0 mg/ml concentration are retest values. Points are means of the last 10 stable sessions under each condition. Brackets indicate the S.E.M. Absence of brackets at a point indicates that the S.E.M. fell within the area occupied by the plotted point. Note that Monkey M-LA was not tested at FRs 128 and 256 and that Monkey M-B was not tested at FR 256.

Fig. 4. Pentobarbital deliveries obtained at FR 32 and above are plotted relative to the number obtained at FR 16. Abscissa: pentobarbital concentration, log scale; ordinate: mean pentobarbital deliveries obtained at FR 32 and above as a percentage of pentobarbital deliveries obtained at FR 16. For each bar on the graph, the denominator is the mean number ($n = 10$) of drug deliveries obtained at FR 16 at that concentration; the numerator is the mean number ($n = 10$) of drug deliveries obtained for the same concentration at the FR value listed. Each percentage was calculated separately for each concentration by dividing the mean number of pentobarbital deliveries at FR 16 into the mean number of deliveries obtained at FR values of 32, 64, and 128. For example, at 2.0 mg/ml Monkey M-LA obtained a mean of 192 deliveries at FR 16 and a mean of 41 deliveries at FR 64; the value for the height of the bar in the figure was calculated by dividing 41 by 192 and then multiplying by 100 (second bar from the right in the top frame). N.T. means not tested. Absence of a bar at the condition also indicates untested conditions.

Fig. 5. Pentobarbital intake (mg/kg of body weight/3-hr session) as a function of pentobarbital concentration and FR size. Abscissa: pentobarbital concentration, log scale; ordinate: mg of pentobarbital consumed per kg of body weight per 3-hr session. Points are the means of 10 sessions.

creased. This analysis reveals an orderly relationship: In general, as FR size increased, drug deliveries as a percentage of baseline were greatest at the highest concentrations and decreased as the drug concentration was reduced.

Drug intake (mg/kg body weight/session) tended to increase directly with increases in drug concentration. With increases in FR size, drug intake at each concentration tended to decrease (Figure 5). Mean intersession water intake did not vary consistently across pentobarbital concentrations or fixed-ratio size.

DISCUSSION

Many findings in the present study are consistent with the results of previous studies. As in previous studies, orally delivered pentobarbital functioned as a reinforcer (DeNoble et al., 1982; Kliner & Meisch, 1982; Meisch et al., 1981). The drug maintained higher response rates and was consumed in larger volumes than its concurrently available vehicle, water. Responding was typical of FR responding maintained by other reinforcers. The inverted U-shaped function between drug concentration and liquid deliveries was noted in an earlier pentobarbital study (Meisch et al., 1981) and has also been observed in studies with orally delivered etonitazene (Carroll & Meisch, 1978, 1980a), phencyclidine (Carroll & Meisch, 1980b), and ethanol (Meisch & Thompson, 1974). Increases in drug intake (mg/kg/session) with increases in drug concentration have also been previously reported (Carroll & Meisch, 1978, 1980a, 1980b; Henningfield & Meisch, 1978; Meisch & Thompson, 1974). Finally, with concentration or dose held constant, a decrease in drug deliveries has frequently been observed with increases in FR size. This occurs both when drug is delivered via the oral route of administration (with, e.g., etonitazene, Carroll & Meisch, 1978, 1980a; phencyclidine, Carroll & Meisch, 1980b; pentobarbital, DeNoble et al., 1982, and Meisch et al., 1981; and ethanol, Meisch & Thompson, 1973) and via the intravenous route (with, e.g., methohexital, Pickens, Muchow, & DeNoble, 1981; and pentobarbital, Goldberg et al., 1971.)

In only a few studies have both FR size and reinforcer magnitude been varied. In

some studies, either two reinforcer magnitudes (Powell, 1969) or two FR values (Goldberg et al., 1971) were investigated. However, Pickens et al. (1981) examined intravenous self-administration of methohexital by rats with four doses and five FR values. When their data are plotted in terms of percentage of baseline, findings similar to those observed in the present study are seen (Figure 6). Thus, it is unlikely that the generality of our findings is limited to a specific species, drug, or route of administration.

The analysis of our results can be related to ideas advanced by Nevin (1974, 1979) concerning the measurement of response strength. He suggested that greater response strength is indicated by greater relative resistance to change produced by some experimental manipulation. Similarly, we think that the greater relative resistance to change in drug deliveries with increases in FR value, observed with increases in drug concentration or drug dose, indicates greater relative reinforcing efficacy. Our study shares some commonalities with that of Nevin (1974), as well as differing from it in some ways. Both studies introduced a change in a controlling variable, with the results expressed and evaluated in terms of proportions of baseline values. The two procedures differed in method. Nevin used a two-component multiple schedule, which provides a within-session control, inasmuch as the compared performances are similarly affected by conditions existing at each experimental session. Our procedure compared operant performances across sessions. A second differentiating feature is the dependent variable for calculating the proportional change. Nevin measured response rate, and defined a more general variable, response strength, in terms of the relative resistance of response rates to change. In contrast, we defined reinforcer strength or efficacy in terms of relative resistance to change of reinforcer-presentation rates. (For a conceptual discussion of reinforcing efficacy as it relates to drugs, see Griffiths, Brady, & Bradford, 1979; for a discussion of practical ramifications, see Schuster, 1975.) The results of our study are

Fig. 6. Methohexital infusions obtained at FRs of 5 and above are plotted relative to the number obtained at FR 1. Abscissa: methohexital dose; ordinate: mean methohexital infusions as a percentage of methohexital infusions at FR 1. For each bar on the graph, the denominator is the mean number ($n = 2$) of drug infusions obtained at FR 1 for a particular dose; the numerator is the mean number ($n = 2$) of drug infusions obtained for the same dose at the FR value listed. Each percentage was calculated separately for each dose by dividing the mean number of infusions obtained at FR 1 into the mean number of infusions obtained at FR values of 5, 10, 15, and 20. For example, at 4 mg/kg Rat 3A obtained a mean of 26 infusions at FR 1 and a mean of 23 infusions at FR 5; the value for the height of the bar in the figure was calculated by dividing 23 by 26 and then multiplying by 100 (far right bar in lowest frame). Note that Rats 3A and 7A were not tested at FR 15.

further evidence that low self-administration rates at higher drug concentrations do not necessarily indicate low reinforcing efficacy of these concentrations.

The conclusion that higher pentobarbital concentrations exhibit greater reinforcing efficacy is supported by the finding that increasingly higher concentrations maintained the highest rates of responding as FR size increased. In the present study, because FR size was varied in an ascending series rather than randomized, this finding might be attributed to the monkeys' development of tolerance to the drug's effects during the course of the experiment. However, evidence against this interpretation is present within each FR concentration series. The number of drug deliveries at the 4 mg/ml retest was approximately the same as that at the initial 4 mg/ml test at each series, and was never substantially higher (Figure 3). If tolerance to the drug were affecting data across FR series, it should also be reflected in higher 4 mg/ml retest values within series.

A possible alternative explanation of our results is that they are simply a function of the baseline rate of liquid deliveries, in that the higher the baseline rate of liquid deliveries, the less will be the percentage of baseline deliveries obtained when FR size is increased. That is, when the response requirement is increased, higher rates of reinforcer deliveries may show proportionately greater decreases than do lower rates. However, this explanation is not consistent

with the results. Figure 4 shows two exceptions at FR 32 to predictions derived from such an explanation. For M-B, a lesser percentage of baseline deliveries was obtained at 0.0625 than at 0.125 mg/ml, though baseline deliveries at 0.125 mg/ml were higher. Also, at FR 16, M-G2 obtained almost identical numbers of drug deliveries at 0.125 and 0.25 mg/ml, but showed a noticeably greater percentage change at FR 32 for the 0.125 mg/ml concentration; an explanation in terms of liquid delivery rate would have predicted equivalent changes.

Similar instances of deviations from dependency-on-rate predictions are present in the results of Pickens et al. (1981). Table 1 lists data for the two highest methohexital doses tested with each animal (the only two doses tested for Rats 3A and 7A), at FR 10 and FR 20. For present purposes, the mean number of infusions obtained at these doses at FR 10 will be considered baseline values. In two cases (Rats 1A and 7A), the number of infusions obtained at the higher dose (4 mg/kg/infusion) was greater; however, for these animals there is a direct relationship between number of baseline FR 10 infusions and percentage of baseline infusions obtained at FR 20, while a dependency-on-rate interpretation would predict an inverse relationship. For each of the other two rats (3A and 6A), the mean numbers of infusions obtained at the two highest doses at FR 10 were approximately equal. At FR 20, however, markedly less percentage change from baseline occurred with the higher dose.

Table 1

Percentage change in methohexital infusions obtained by rats from FR 10 to FR 20 (Pickens et al., 1981).

Methohexital dose (mg/kg/infusion)	Rat 1A		Rat 6A		Rat 3A		Rat 7A	
	3	4	3	4	2	4	2	4
Mean number of infusions at FR 10	31.0	37.0	32.0	30.5	24.5	23.5	17.5	20.5
Mean number of infusions at FR 20	6.5	20.0	9.5	23.5	9.5	17.0	7.5	17.0
Infusions at FR 20 as a percentage of infusions at FR 10	21	54	30	77	39	72	43	83

Again, these results are not consistent with the dependency-on-rate hypothesis.

In the present study there are few data points where opposite predictions are made by the two hypotheses: relative reinforcer efficacy versus dependency on rate. An objective of future research will be to differentiate between these alternatives. In this regard it will be important to measure multiple points on the ascending as well as the descending limb of the concentration-delivery rate function. Then concentrations from both ends of the function that generate similar rates can be compared.

Our results with pentobarbital and those of Pickens et al. (1981) with methohexital show that use of relative changes in number of reinforcers obtained may be more useful than measures of absolute rate when comparing behavior maintained by different magnitudes of a reinforcer. For example, in the present study at FR 16 and concentrations of 0.125 and 0.25 mg/ml, high rates of drug delivery occurred (Figure 3). On the basis of absolute rates, one might conclude that these concentrations were maximally effective as reinforcers—a conclusion not supported by the results obtained at larger FR values. Thus, examination of absolute reinforcer-delivery rates, or of behavior at only one schedule value, may not be sufficient for evaluating the reinforcing efficacy of different drug doses or concentrations. Rather, investigation of relative changes in behavior over an extended range of parameter values appears to be an important strategy to follow.

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