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Intravenous Diazepam in Humans: Effects on Acquisition and Performance of Response Chains[1]

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DESJARDINS, P. J., J. M. MOERSCHBAECHER, D. M. THOMPSON AND J. R. THOMAS. *Intravenous diazepam in humans: Effects on acquisition and performance of response chains.* PHARMAC. BIOCHEM. BEHAV. **17**(5) 1055–1059, 1982.—A technique based upon an individual-subject design was used to investigate the effects of intravenous diazepam on the acquisition and performance of response chains in humans. In each of two conditions subjects were required to emit a different sequence of ten responses in a predetermined order on three levers. The conditions alternated within each session under a multiple schedule. In the performance condition the sequence of responses was the same each session. The second condition was a repeated-acquisition task. In this condition subjects were required to learn a different sequence of responses each session. Diazepam produced dose-dependent decreases in the overall rate of responding in each subject under both conditions. In two of the three subjects tested, errors were increased in the learning condition at doses lower than those required to disrupt accuracy in the performance condition. In one subject, accuracy in both the learning and performance conditions was equisensitive to the disruptive effects of diazepam. These data are consistent with the effects of the benzodiazepines in analogous animal procedures. Furthermore, the data suggest that the behavioral effects of intravenous diazepam may exhibit marked variations across subjects at clinically relevant doses (5–10 mg).

Repeated acquisition Response chains Multiple schedule Diazepam Lever press Humans

DIAZEPAM has been reported to produce a variety of behavioral effects [15,16]. In addition to producing "psychomotor" and "anterograde memory" deficits, diazepam has also been reported to disrupt learning [11, 12, 13]. Most studies of diazepam's effects on learning have utilized an independent-groups design and investigated only a single dose [15,16]. In addition to the limitations inherent in a single-dose study, the generalization of these data may be limited by intersubject variability in either performance on the behavioral task itself, or by large variations in pharmacological variables such as the kinetics of diazepam [1,14]. In investigating the effects of a drug on learning, an "individual subject" design has several important advantages over the more conventional "independent groups" design [3]. Among these are the elimination of intergroup variability, the direct behavioral measurement of individual performance (versus statistical derivations), and the direct applicability of the findings to the behavior of the individual.

The effects of the benzodiazepines and a wide variety of other drugs on learning have been investigated in animals using an individual-subject design and the technique of repeated acquisition. Generally it has been found that the acquisition of a complex discrimination is more sensitive to the disruptive effects of a drug than is the performance of such a discrimination [18]. The purpose of the present study was twofold: (1) to determine whether this same technique could be successfully applied to the study of drug effects on learning in humans and (2) to determine whether diazepam might selectively affect the acquisition of a complex discrimination involving response chains.

METHOD

Subjects

Three caucasian male volunteers, weighing 70.5–71.8 kg, who were between 24 and 25 years of age participated. A

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fourth subject (S2) withdrew from the study during the first week. Each subject was enrolled in dental school. Prior to the start of the study each subject was given a physical examination and signed a consent form in which the general nature of the study was described and possible risks outlined.

Apparatus

The response panel consisted of a sloped cabinet measuring 22.7×45.6×20.5 cm, mounted on an adjustable tray directly in front of the subject. Mounted on the vertical front of the cabinet were three levers spaced 15.5 cm from the edge of the cabinet and 7.5 cm apart. Each lever required a downward force of 200 g for activation. Three stimulus display units (Industrial Electronic Engineers, North Hollywood, CA) were mounted 10 cm above each lever (7.5 cm apart, center to center) on the sloped front of the cabinet. A digital counter was mounted on this same surface 7.5 cm from the top and 4.5 cm from the right edge of the cabinet. Three pilot lamps (green, orange and red) were vertically aligned 3 cm apart (center to center) and 4 cm from the center of the left stimulus display unit. The orange lamp was not used in the present study. An additional pilot lamp was mounted 4 cm from the top and 9 cm from the left edge of the cabinet. Solid-state scheduling and recording equipment was located in the same room out of the direct view of the subject.

Baseline Procedure

The baseline procedure consisted of a multiple schedule of repeated acquisition and performance of behavioral chains. In each component of the schedule, the subject was required to emit a different sequence of ten responses in a predetermined order on the three levers. One of ten numbers (0–9) was projected on the center stimulus-display unit. The subject's task was to press a particular lever in the presence of each number, e.g., 0-Left correct; 1-Right correct; 2-Center correct; 3-Right correct; etc. When the sequence was completed, the stimulus-display was briefly turned off and the counter was incremented by one. When the subject pressed an incorrect lever (e.g., the left or right lever when the center lever was correct) the error was followed by a 2-sec timeout. During the timeout, all stimuli were turned off and responses had no programmed consequences. An error did not reset the sequence; i.e., the number displayed after the timeout was the same as before the timeout. In the performance component of the multiple schedule, the green pilot lamp was illuminated and the sequence of ten responses was the same each session (Left(L)-Right(R)-Center(C)-R-L-R-C-L-C-R). In the learning component of the multiple schedule, the red pilot lamp was illuminated and the subject was required to learn a different sequence of ten responses each session. For example, during one session the sequence was C-L-R-L-R-C-L-R-C-L, while in the next session the sequence was R-C-L-R-L-R-C-L-R-C. The sequences were chosen with the following restrictions. The performance sequence was never used in the learning component. In any sequence each of the three lever positions occurred 3 or 4 times and no two consecutive responses were the same. For any two consecutive sequences, position repetitions did not occur in any of the ten positions.

The components of the multiple schedule alternated after 20 sequences were completed or 15 min, whichever occurred first. For each subject, each session began in the same component (subject 1 in performance and subjects 3 and 4 in learning). Each session was terminated after 120 sequences (60 in each component). The data for each session were analyzed in terms of (a) the overall response rate (total responses/min, excluding timeouts) in each component expressed as the percent of control and (b) the overall accuracy or percent errors ((errors/total responses) × 100) in each component. In addition to these measures based on session totals, within-session changes in responding were monitored by a cumulative recorder. For example, acquisition of the response sequence in the learning component was evidenced by within-session error reduction.

General Procedure

Subjects were first trained on the performance chain and then on the multiple schedule. Prior to drug testing, error levels in both components of the multiple schedule were allowed to stabilize (10–12 sessions). Following preliminary training, each subject was run a maximum of two days a week (a treatment and a baseline control day) at approximately the same time. On each day two sessions were conducted. The sessions were separated by a period of 10 min. Subjects were seated in a dental chair and their nondominant arm restrained. The subject was permitted to adjust the location of the response panel to a comfortable position, blood pressure and pulse rate were recorded, and the room lights were dimmed prior to the start of each session. Each day, before the start of the first of the two sessions, the following instructions were read to the subject:

In this experiment, your task involves pressing the three levers (in front of you) in a particular sequence. Press only one lever at a time with your preferred hand. Every time you complete a sequence of ten correct responses, the counter advances. Your goal is to get the counter to advance as quickly as possible. Above the three levers is a display unit on which one of ten numbers is presented. The number 0 will be presented at the beginning of the sequence. When you make your first correct response, the number will change from 0 to 1. When you make your second correct response, the number will change from 1 to 2, and so on until the sequence of ten correct responses is completed. If you make an error, the number display will turn off for 2 seconds. Do not respond on the levers when the number display is off. The green light indicates a performance condition, in which the sequence is the same from session to session. The red light indicates a learning condition, in which the sequence is different from session to session. The green and red lights will alternate during each session.

After the instructions were read to the subject, a "warm-up" period was conducted which required 20 completions of the performance sequence. Approximately 5 min later the first session began. Subjects were paid a fixed amount ($30) for each day they participated in the study.

Drug Testing

On treatment days, diazepam or its vehicle was injected into a large vein of the restrained arm of the subject, in a single-blind manner, approximately 5 min prior to the start of the second session. Each subject received an initial dose of 5 mg and subsequent doses were then selected on the basis of the behavioral effects of this dose and administered in a mixed order. The vehicle and three doses of diazepam were studied in each subject. The approved clinical protocol limited the study to a maximum of four drug injections per subject. Therefore, only a single dose was repeated in two of the

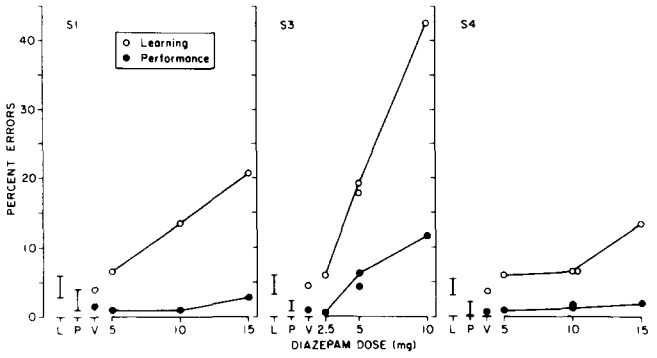

FIG. 1. Effects of varying doses of diazepam on percent errors in the learning and performance components of the multiple schedule for each subject. The vertical lines at L (learning) and P (performance) indicate the range of seven baseline control sessions. The data points above V indicate the effects of vehicle administration. The unconnected points at 5 and 10 mg represent redeterminations.

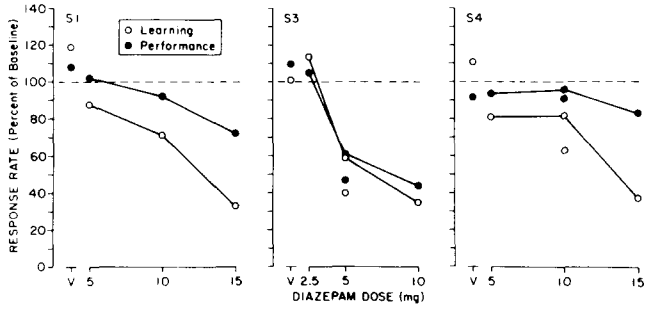

FIG. 2. Effects of varying doses of diazepam on rate of responding in the learning and performance components of the multiple schedule for each subject. Data for the vehicle (V) and each dose determination are expressed as percent of control of that baseline session which preceded each injection. Unconnected points represent a second determination at a given dose.

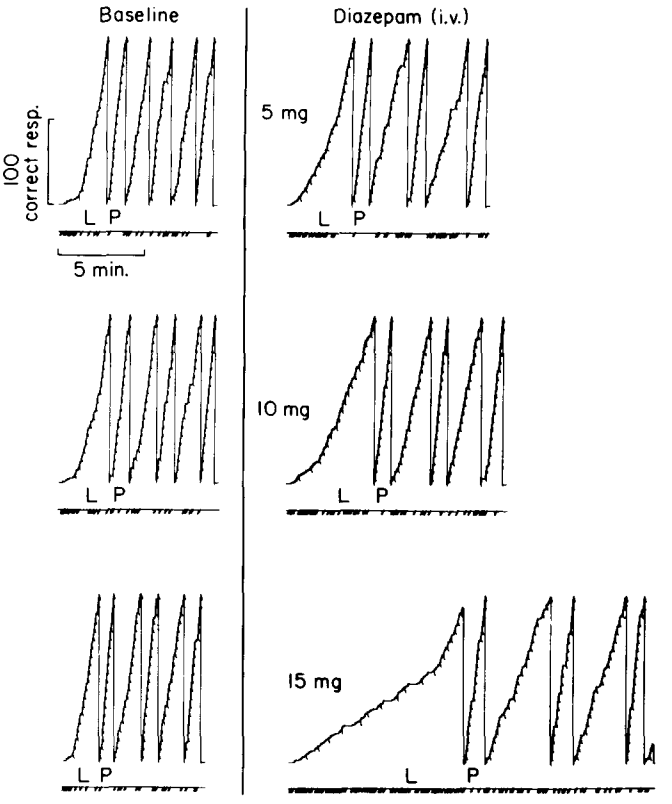

FIG. 3. Cumulative records illustrating the within-session pattern of responding of subject 4 during both baseline and diazepam sessions. The response pen stepped upward with each correct response and was deflected downward each time the 10-response sequence was completed. Errors are indicated on the event pen (below each record), which was held down during each timeout. The stepping pen reset each time the components changed.

subjects. Treatments were separated by at least one week. The volume of each injection was 4 cc infused over a period of 4 min. The vehicle consisted of propylene glycol (40% v/v), ethanol (10%), sodium benzoate (2.5%), benzoic acid (2.5%), and benzyl alcohol (1.5%).

RESULTS

The effects of varying doses of diazepam on percent errors in the learning and performance components of the multiple schedule are shown for each subject in Fig. 1. The range of errors in each component for seven baseline sessions are shown at the left of each panel. For each subject, under baseline conditions, percent errors were greater in the learning (L) than in the performance (P) component. The data for the diazepam vehicle alone (V) fell within these baseline ranges for each subject. Increasing doses of diazepam generally increased errors in each of the subjects. In two of the subjects (S1 and S4) the error-increasing effects of diazepam were selective in that errors were increased in the learning component at doses which had no effect on errors in the performance component. For example, in subject S1, doses of 10 and 15 mg increased errors in the learning component without affecting accuracy in the performance component. Though the absolute error-increasing effects were smaller in subject S4 than in subject S1, the nature of the selective drug effect was the same. Errors were increased in learning but not in performance at doses of 10 and 15 mg. In subject S3, however, accuracy in both the learning and performance conditions was equisensitive to the disruptive effects of diazepam. Errors in both components were increased with increasing doses of diazepam; large error-increasing effects occurred at doses of 5 and 10 mg in both components. On a mg basis this subject was also the most sensitive to diazepam.

The effects of diazepam on rate of responding in the learning and performance components of the multiple schedule are shown for each subject in Fig. 2. The diazepam vehicle alone (V) had little or no effect on response rates in any of the subjects. Similarly, in each subject the lowest dose tested (2.5 or 5 mg) had virtually no effect on rate of responding in either component. In subjects S1 and S4, response rate was slightly decreased in learning but not in performance at the 10 mg dose. The 15 mg dose produced greater rate-decreasing effects in these same subjects. While the rate of

responding was decreased in both components at this dose, the rate-decreasing effect was greater in the learning component. In subject S3, doses of 5 and 10 mg produced substantial decreases in response rate in both the learning and performance components.

The dose-related effects of diazepam on the within-session pattern of responding of subject S4 are shown in the cumulative records of Fig. 3. Three baseline sessions are shown in the left panel. The response pen stepped upward with each correct response and was deflected downward each time the 10-response sequence was completed. Errors are indicated on the event pen, which was held down during timeout. When the components changed, the stepping pen reset and began a new excursion. Since the two components alternated during the session, the first, third, and fifth excursions represent responding under the learning (L) condition. A prominent feature of the baseline data is the rapid within-session error reduction during the first learning (L) component. This is indicated by a decreased frequency of deflections of the event pen. In comparison, the error rate in the performance (P) component was lower and was relatively constant during each baseline session. The effects of three doses of diazepam, for this same subject, are shown in the right panel of Fig. 3. With the 5 mg dose, there was a small error-increasing effect in the learning component, whereas accuracy in performance was unaffected. The selective nature of the drug effect, between learning and performance, was more evident at the 10 mg dose (compare the frequency of errors in learning and performance during each excursion). After 15 mg of diazepam, there was a large error-increasing effect in learning (although some within-session error reduction still occurred) and a slight increase in performance errors. The rate of responding was also noticeably decreased in both components at this dose.

DISCUSSION

While there have been relatively few studies of the effects of drugs on schedule-controlled behavior in humans, the results are generally similar to those obtained in animals [6, 9, 10, 19]. For example, in animals antianxiety drugs, such as diazepam, increase punished responding at doses which have little or no effect on unpunished responding [5]. Similarly, in humans, diazepam has been reported to selectively increase responding suppressed by either electric shock [2] or monetary loss [4]. The results of the present study extend the empirical data base of this generalization to the acquisition and performance of a complex discrimination.

In each subject tested, diazepam produced dose-dependent decreases in the rate of responding in each component. While the results from previous studies of diazepam's behavioral effects in humans are somewhat inconsistent, these rate-decreasing effects are generally comparable to those reported for tasks involving "reflex speed" or "vigilance" [15]. For example, in several studies which used a letter cancellation task, it was found that diazepam decreased the number of cancellations attempted or completed but did not affect the number of errors [7,8]. Similarly, in the present study, two of the subjects (S1 and S4) exhibited decreases in response rate in the performance component at doses which did not affect accuracy.

In humans, diazepam has been reported to disrupt the acquisition but not the performance of a variety of tasks [11, 12, 13]. For example, in a study using an independent-groups design, a single dose of intravenous diazepam (0.3 mg/kg) was found to impair the acquisition of a series of lists of nouns, but not the reporting of different lists which had been learned prior to drug administration [11]. The present data, obtained with an individual-subject design, extend this finding across a range of doses. In two of the three subjects tested, diazepam selectively disrupted accuracy in the learning component without affecting accuracy in performance. The selective nature of the error-increasing effects in learning produced by diazepam in these subjects is comparable to that previously reported for the benzodiazepines in animals [17]. The mechanism for this selective drug effect on learning has been related to the relatively weak control over the behavior by environmental stimuli [18]. In one subject (S3), however, accuracy in both the learning and performance conditions was equisensitive to disruption at the doses tested. The data from this subject would suggest that the behavioral effects of intravenous diazepam may exhibit marked variations across subjects at clinically relevant doses (5–10 mg). A similar non-selective effect may have been obtained in the other subjects had higher (>15 mg) doses been investigated. In animal studies using the technique of repeated-acquisition, such selective drug effects on accuracy in learning have been reported to be dose-dependent [18]. Taken together the present data for both accuracy and rate suggest that neither variable alone can completely characterize the effects of diazepam on complex behavior. In other words, dose-effect data reflecting both the "quality" and "quantity" of the behavior are necessary to profile the drug effect.

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