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Behavioral Effects of Oral Versus Intravenous Administration of Diazepam[1]

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GHONEIM, M. M., S. P. MEWALDT AND J. V. HINRICHS. *Behavioral effects of oral versus intravenous administration of diazepam.* PHARMACOL BIOCHEM BEHAV 21(2) 231–236, 1984.—The behavioral effects of oral versus intravenous administration of diazepam were studied in 50 volunteers using a battery of memory, cognitive, mood and psychomotor tests repeated over a 4.5 hr period. Subjects received diazepam 0.2 mg/kg or placebo as capsules, commercial tablets or intravenous solution in a randomized double blind manner. While a quick onset of effects occurred with intravenous administration followed by the capsule and tablet oral administrations in that order, the recovery rate was similar for the 3 methods of administration. Contracy to many claims in the literature the effects of oral administration were substantial. Behavioral impairment was directly related to the magnitude of the memory component of the task. On many of the tasks the pattern of diazepam impairment was one of delayed improvement of performance, a pattern which would only be apparent with repeated testing. Subjects who received diazepam showed a paradoxical enhancement of recall for material learned before the drug.

Cognition Diazepam Learning Memory Method of administration Psychomotor performance

DIAZEPAM (Valium) is administered to patients by the oral or intravenous routes. It is usually given intravenously before endoscopies, oral surgical procedures, cardioversion and regional anesthesia, for induction of general anesthesia, and for the management of status epilepticus. The drug is prescribed orally for the treatment of anxiety and insomnia, preanesthetic medication and for the relief of muscle spasticity. Oral administration naturally slows the achievement of adequate drug concentration in the brain compared to the intravenous route. There are indications that the drug absorption rate or the rate of change of drug levels are important determinants of the magnitude of effects produced by diazepam. McLeod and his associates [16] found that the extent of psychomotor impairment attributable to a single oral dose of diazepam is greater on the "upswing" of the plasma concentration-time curve than on the "downswing" part, even though plasma levels at the time of testing may be similar. Greenblatt and his colleagues [8] observed that subjective perceptions of sedation and reduction in speed and clarity of thought following 25 mg oral doses of chlordiazepoxide, a closely related benzodiazepine, depended more upon the rate at which blood levels were achieved following the dose than upon the blood level measured at the time the subjective effect was assessed. Kortilla *et al.* [14] found that a rapid intravenous injection of diazepam (0.15 mg per kg over 20 sec) induced greater sedative and amnesic effects than a slow injection (over 120 sec) of the same dose.

Kothary *et al.* [15] concluded that the memory effects of oral versus intravenously administered diazepam were "remarkably different." This view is also shared by a recent reviewer of the drug actions [12]. The manufacturer of diazepam uses the same logic in the medical advertisement and promotional material for the drug [21]. It is our impression that many physicians subscribe to the views that oral administration of diazepam has no effect on memory function [9,24].

The present study compares the behavioral effects of the drug after intravenous and oral administrations, using a wide battery of tests that included learning and memory, cognition, psychomotor and mood tests. Since all valid investigations of the human behavioral effects of the drug following its oral administration use a double-blind procedure, this usually entails dispensing the drug in capsules. The pharmacokinetics of the drug administered as capsules may be different from those of commercially-available tablets since the rate of dissolution of the two formulations in the upper bowels may be different. We therefore included in the study a comparison between the capsules and commercially-available tablets. The effects of the drug were followed for more than 3.5 hr after its administration.

METHOD

Subjects

Fifty healthy paid volunteers taking no medications and ranging in age from 18 to 30 years participated in the study. All subjects had at least one year of college education. Subjects beyond 20 percent of their ideal body weight and those with excessive consumption of alcohol and/or marijuana were excluded.

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Treatment

Diazepam 0.2 mg/kg was administered as capsules (which contained the active drug with lactose as a filler), commercially available "Valium" tablets, or as an intravenous solution (5 mg per ml). By the use of various strengths of capsules and tablets, the discrepancy between the dose administered and that matched to body weight was within 10 percent. Placebo capsules containing only lactose served as a control for the oral medication and saline solution was the control for the intravenous injection of diazepam.

Subjects who received oral medications were given their treatments individually away from the view of other subjects. Those receiving tablets were unaware that others received capsules and vice versa. Subjects who received intravenous medications were injected with the solution at the rate of 1 ml per minute while lying supine in bed, i.e., a 70 kg subject received the medication over a 3 min period.

Procedure

The five treatment groups contained ten subjects each: five males and five females with the exception of the placebo intravenous group which contained six males and four females. Treatments were assigned randomly and subjects were tested in groups averaging five subjects each, under double blind conditions.

Subjects were instructed to get a good night's sleep before participation in the experiment and to abstain from marijuana and alcohol for at least 24 hours prior to their session. They arrived, fasting, at 7 a.m. at the laboratory. The session began with general instructions about the procedure, signing of consent forms and practice on each of the tests. Subjects then received the drug treatments. The postdrug tests were administered in four testing periods separated from one another by rest periods of varying length. The order of the tests and their relative time of administration are summarized in Table 1. At the third postdrug break, 160 min after treatment subjects were given a snack. A description of the tests employed is reported below.

Tasks

Immediate free recall. Subjects were presented with a different 24-item list of words at each of the five test periods. The lists consisted of 24 nouns, presented as slides at a rate of one slide every 2 sec. The nouns were selected from the Paivio *et al.* [20] norms to have ratings of imagery and concreteness greater than 5.0, ratings of meaningfulness greater than 5.97 and, according to the Thorndike and Lorge norms [23], frequencies greater than 49 per million. Immediately after the last item in each list was presented, subjects were given 2 min to write in any order as many of the words as they could remember.

Delayed free recall. At 180 min following drug administration, subjects were asked to write in any order as many of the words as they could remember from each of the four previous free recall lists, i.e., the practice and first three postdrug lists. (Note: The last free recall list had not yet been presented.) Five min were allowed for recall.

Serial number learning. At each of the five testing periods, subjects were presented with a different 15-digit serial list. Each sequence was presented three times at a rate of one digit per sec. Immediately after each presentation subjects were given 30 sec to write as many digits as they could remember on a sheet containing a row of 15 boxes. They were told that their score would be determined by the number of digits they had recalled in their correct positions.

Mood evaluation and cognitive booklet. Subjects completed a different cognitive booklet at each of the five testing periods. Each booklet began with a mood evaluation form, and was followed by a series of cognitive tasks: addition, sequence completion, and two-target symbol cancellation. The cognitive tasks each consisted of one page of material that subjects worked on for one min.

Mood evaluation. Subjects rated their feelings on ten scales derived from Norris [19]. The ends of each of the seven-point scales were marked by adjectives representing the extremes of the dimension being rated: alert–drowsy, calm–excited, fuzzy–clear headed, well coordinated–clumsy, mentally slow–quick witted, energetic–lazy, incompetent—capable, attentive—dreamy, tense—relaxed and interested–bored.

Addition. Each page in the addition task contained six columns of single-digit numbers. For each column of numbers, subjects were to add each successive pair of numbers, i.e., to add the first and second number, the second and third, etc., and to write the sum to the right of the column.

Sequence completion. This task tested the subject's ability to detect a pattern within a string of letters [22]. Subjects were presented with a string of letters (ranging in length from 10–14 letters) and were required to complete the string by determining the next four letters in the sequence. Each time the task was presented, subjects were given three sequences to attempt in the time allotted.

Symbol cancellation. Subjects were presented with several rows consisting of a pair of target letters followed by a string of 60 upper case letters [10]. For each letter string, subjects were instructed to cross out every instance of the two target letters.

Tapping. Subjects used one or two fingers of their dominant hand to press the spring-loaded button on a mechanical counter. They tapped as rapidly as possible for two 30 sec trials which were separated by a 30 sec rest period.

Three other tasks; semantic categories, card rotation and postural stability were used but are not described here. The effects of diazepam on these tasks have been described before [5,6] and performance on these tasks did not vary as a function of the method of administration.

Analysis of variance was used to analyze the results of each task. The factors included in the analysis were test time relative to drug administration (exact times varied with each task; Table 1) and treatment (placebo and diazepam administered by three methods).

RESULTS

Free Recall

Immediate free recall. Predrug performance revealed no differences among the five groups. Analysis of postdrug data showed that the effects of relative test time, $F(4,160)=17.59$, drug group, $F(4,40)=7.07$, and their interaction, $F(16,160)=4.33$, all produced significant effects, $p<0.001$ in all cases. The two placebo groups did not differ, $F<1$. Further comparisons confirmed that the interaction was the result of significant differences among the drug groups at the first test interval (+20 min), $p<0.01$. Relative to subjects receiving capsules, administering diazepam by injection produced greater memory decrements and giving diazepam by tablet produced less memory impairment, 20 min after administration. However, there was no difference in re-

TABLE 1
SCHEDULE FOR THE STUDY

Time	Task
−60	Instructions and Practice
00	Drug Administration and Break (20 min)
+20	Free Recall
+24	Number learning 1
+32	Cognitive Booklet 1 with Mood Evaluation
+39	Tapping 1
+41	Break (5–10 min)
+50	Free Recall 2
+54	Number Learning 2
+62	Cognitive Booklet 2 with Mood Evaluation
+69	Tapping 2
+101	Break (5–10 min)
+110	Free Recall 3
+114	Number Learning 3
+122	Cognitive Booklet 3 with Mood Evaluation
+129	Tapping 3
+161	Break (Snack)
+180	Delayed Free Recall (5 min recall)
+186	Break (10–15 min)
+200	Free Recall 4
+204	Number Learning 4
+212	Cognitive Booklet 4 with Mood Evaluation
+219	Tapping 4

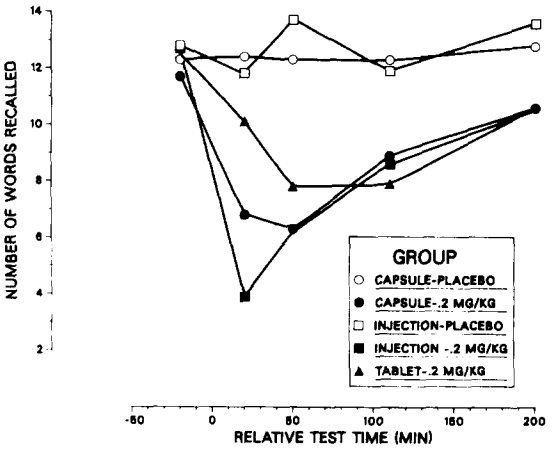

FIG. 1. Immediate free recall from 24-word lists. Zero was the time of drug or placebo administration.

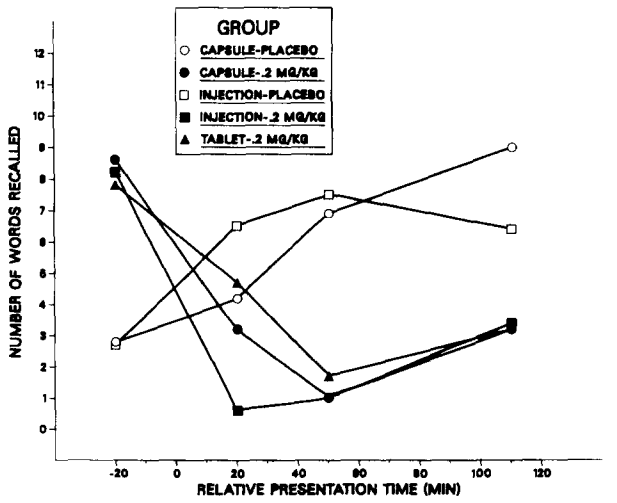

FIG. 2. Delayed free recall of words from one pretreatment and three posttreatment lists. The times of presentation of the four lists are shown. Zero was the time of drug or placebo administration. The time of recall was 180 min posttreatment.

covery performance over the last three tests (+50 to +200 min), $F<1$ (Fig. 1).

Delayed recall. An overall analysis of variance for the five groups demonstrated relative presentation time, $F(3,120)=8.26$, $p<0.001$, and drug group effects, $F(4,40)=3.57$, $p<0.02$, as well as a significant interaction between these two variables, $F(12,120)=11.70$, $p<0.001$. Follow-up analyses showed that the two placebo groups did not differ from each other, $F<1$. In addition, consistent with the results of immediate free recall, the three drug groups differed only in the delayed free recall of the first list presented after drug administration (+20 min). That is, performance of the diazepam injection group was worse than the capsule group and the latter was worse than the tablet group. Once again, however, the recovery functions were virtually identical (Fig. 2). In marked contrast to the delayed recall of words learned under the influence of diazepam, drugged subjects recalled significantly more words from the pretreatment list than the placebo subjects, $p<0.001$. Subjects in the two placebo groups recalled fewer than 3 of 24 words presented 3 hours earlier, while diazepam-treated subjects, regardless of the method of administration, recalled a mean of more than 8 words.

Number learning. Factors included in the analyses of this task were trial number (1–3), sex, and time of testing relative to drug administration (−15, +24, +54, +114, and +204 min). Although performance on the number lists presented before drug administration did not differ among groups, $F(4,40)=1.38$, $p>0.25$; there was a significant interaction between drug group and relative test time, $F(16,160)=3.18$, $p<0.001$, caused by postdrug performance differences. Both placebo groups exhibited immediate improvement on the first postdrug set of trials. The diazepam capsule group showed no improvement until Time +114. The diazepam injection group had a significant drop in performance on the first postdrug test, $p<0.001$, and then exhibited about the same recovery pattern as the diazepam capsule groups. The tablet group was somewhat surprising. The failure to improve on the first two postdrug tests was comparable to capsule performance, but then performance dropped on the third test, nearly two hours after administration, before showing recovery at Time +204.

Mood evaluation. In addition to analyzing each individual scale, a composite scale was constructed by summing the

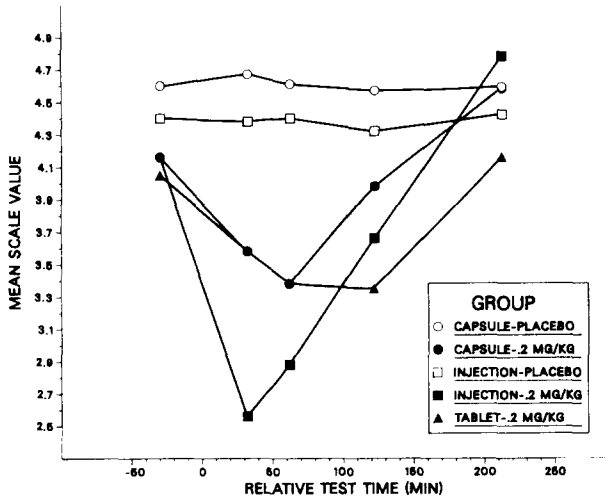

FIG. 3. Subject's mood evaluations represented by a composite scale. Zero was the time of treatment.

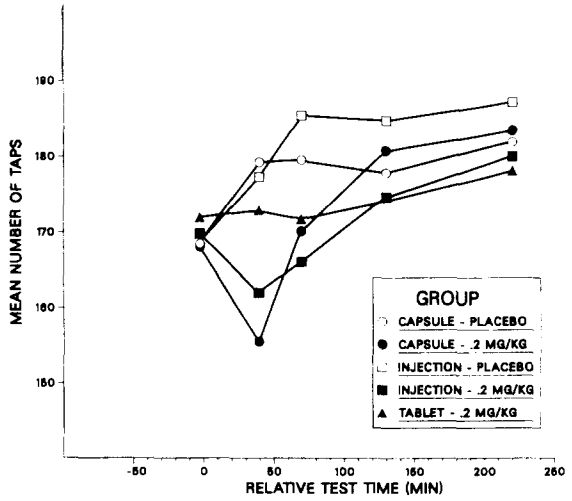

FIG. 4. Total number of taps as a function of treatment condition and time. Zero was the time of treatment.

scores on all the scales. Predrug comparisons showed no significant differences among the groups. Postdrug effects are summarized in Fig. 3. All active treatment groups showed an initial decline in mood evaluation compared to the two placebo groups followed by an increase at approximately the same rate across all three methods of administration, $F(16,180)=4.53$, $p<0.001$. Although the figure suggests that the decrease in subjective impressions was greater in the diazepam injection group and lower mood scores were somewhat more persistent in the tablet groups, statistical analysis revealed no significant interaction with method of administration.

Other Cognitive Tasks

Addition. Two dependent variables were examined: the number of addition problems completed and the proportion of the completed problems that were correctly answered. Analysis of both variables indicated no significant effects nor interactions at the predrug test, $p>0.1$. Analysis of the postdrug data revealed no significant effects for the proportion correct. However, for the number of problems attempted there was a significant main effect for relative test time, $F(4,180)=17.05$, $p<0.001$. Overall, subjects improved at the task with each repetition. In addition, there was a significant Relative Test Time × Drug Group interaction, $F(16,180)=1.79$, $p<0.05$. Follow-up analyses showed immediate improvement in the placebo groups and delayed gains in the drug groups over successive tests. At the second postdrug test, the diazepam capsule group was significantly impaired relative to the other groups with the diazepam injection group beginning to improve, $p<0.05$.

Sequence completion. The data were scored in terms of the total number of letters the subjects wrote which were correct and the total number of responses which were errors. This task proved to be insensitive to the effects of diazepam.

Symbol cancellation. Three response measures were considered for analysis: the number of lines of stimuli on which the subject responded, detection rate (calculated by taking the number of targets a subject detected and dividing by the total number of targets which appeared in the lines scanned), and false alarms. Because the false alarm rate was exceedingly low, this response measure was not analyzed. The analysis of predrug performance indicated no significant effects for either of the other two dependent variables, $p>0.2$, in each case. Analysis of number of lines attempted for postdrug effects indicated a significant main effect for relative test time, $F(4,180)=22.32$, $p<0.001$. Subjects generally became faster at the task each time it was repeated. More importantly, there was a significant Relative Test Time × Drug Condition interaction, $F(16,180)=1.84$, $p<0.05$. As with the addition task, the effect of diazepam was to delay the improvement resulting from practice. At the first postdrug test, the performance by the capsule and injection diazepam groups was poorer than the other three groups, $p<0.05$. At the second postdrug test, all three diazepam groups were impaired relative to the two placebo groups, $p<0.05$. Later tests showed recovery and no significant differences, $p>0.05$, but with the tablet group lagging behind. Detection rate, the other dependent variable, was not sensitive to the drug manipulation, $p>0.2$.

Tapping. Performance was identical across all groups prior to drug administration, $F<1$, with one exception: males tapped faster than females (185.0 vs. 164.0 mean taps per trial), $F(1,96)=50.36$, $p<0.001$. Postdrug analysis showed a significant main effect for relative test time, $F(4,180)=13.71$, $p<0.001$. Subjects performed faster over the course of the session. Of more interest is the significant Drug Group × Relative Test Time interaction, $F(16,180)=2.33$, $p<0.01$. This interaction is displayed in Fig. 4. The diazepam capsule and injection groups displayed the largest decline in performance at the first postdrug test, while the tablet group showed little change at this test. In fact, drug effects in the tablet group again appeared as a failure to improve over repeated tests rather than as a drop from predrug performance levels.

DISCUSSION

The behavioral effects of diazepam following each

method of administration were substantial and quite similar. Every task which was sensitive to intravenous administration was also sensitive to the drug by the oral route. However, each method of administration of diazepam exhibited a particular time course of drug action for several memory and cognitive tasks. A quick onset of drug effects occurred with intravenous administration, which was followed by the capsule and tablet oral administrations in that order. The maximum effects after the tablet administration were occasionally delayed for more than one hour as in the serial number learning task. Nevertheless, the recovery rate on most of the tasks was similar for the three methods of administration.

The results seem logical from the pharmacokinetic viewpoint, because when absorption of a drug is rapid relative to its elimination, as in the case of diazepam, the peak effect after oral dosage approaches that achieved after intravenous administration [17]. Kaplan *et al.* [13] and Baird and Hailey [1] compared the pharmacokinetic profile of diazepam following intravenous and oral administrations. During the first hour, the drug concentration in the blood following intravenous injection rapidly declined while it rapidly increased following the oral route. After this time, the concentrations following either method of administration were very close to each other. The time course of the behavioral impairment produced by the drug in the present study followed a similar course, perhaps reflecting sensitivity to drug levels in the body.

Our results are different from other investigators who could find no memory or behavioral impairment after oral diazepam [9, 15, 24]. This may be due to several factors. Many of these studies were done with no placebo control, biased (non-blinded) observers and subjects, and with the confounding effects of surgery, anesthetics and sedative-analgesic drugs given during the operation and afterwards (most of the subjects were patients who had anesthesia and surgery). Sex differences were usually not considered and a fixed dose was administered irrespective of body weight. The tests lacked sensitivity, standardization, and did not allow easy comparison across methods of administration.

It should be noted that in most of the previous studies referred to in the previous paragraph, subjects were shown some pictures and were asked to recall them about 24 hours later. A question may therefore be asked whether this longer time interval, compared to the present study, could account for the discrepancy between the conclusions in the literature and those of the present study. To give an answer, one needs to understand the mechanism of action of diazepam and the effect of a long recall interval on the sensitivity of the tests. Drugged subjects in the present study displayed large performance deficits in both immediate and delayed free recall of lists learned after drug administration. However, in the delayed recall of lists learned prior to drug administration, drugged subjects actually recalled significantly more items than placebo subjects. This data strongly suggests that diazepam impairs acquisition of new information, while leaving retrieval processes intact. If diazepam impaired retrieval, recall of both pre- and postdrug should be affected. Because memory retrieval processes are not affected by the drug, the length of the retention interval should not be important in demonstrating drug induced deficits in memory. What is crucial in demonstrating the impairment of diazepam on memory is that acquisition occurs after drug administration. The other consideration relates to the sensitivity of the tests with a 24 hour delay. It is probable that this would have resulted in low performance, possibly a floor effect, by all groups including placebo and made interpretation of the results very difficult.

As mentioned above, in delayed free recall, subjects who received diazepam recalled the predrug word list better than those who received placebo. This enhancement of recall for material learned before the drug is similar to results obtained by our group [18] and by other groups of investigators [2,3]. The increase is probably best explained as a consequence of reduced interference in the diazepam treated groups. Because of their poor learning of the posttreatment lists, drugged subjects had little material to interfere with their recall of the pretreatment list (manuscript is under review).

The degree of impairment produced by diazepam varied systematically across cognitive tasks, in a manner suggesting the tentative interpretation that degree of impairment was directly related to the magnitude of the memory component of the task. More specifically, the greater the need for acquisition of new information or skills, the greater the observed impairment in performance. Thus performance in the free recall memory task, which directly tested new learning, was the most sensitive indicator of the behavioral effects of the drug. In addition, the two tasks, addition and symbol cancellation, which had a learning component as practice effect (demonstrated by placebo subjects improving with each repetition of the task), were also sensitive to the effects of the drug. In contrast, repetition of the sequence completion task produced no practice effect and correspondingly was not sensitive to the drug.

In a similar pattern to the practice effects, the influence of diazepam on the serial number learning and the tapping task was mainly one of delaying improvement of performance. Subjects were less able to benefit from previous practice while under the influence of the drug. For example, in Fig. 4, which displays the results of the tapping task, subjects receiving tablets did not show a decline from their predrug performance level. However, they failed to show improvement during the first three posttreatment sessions as was apparent in the placebo groups. The critical point is that the drug effect appeared in these tasks not as a decline in performance from predrug levels, but rather as a failure to show improvement in performance over trials, until presumably the drug concentration in the brain declined to levels which allowed recovery. This type of performance decrement would be missed if subjects were not repeatedly tested and may be one of the reasons for the conflicting literature on the behavioral effects of the drug.

The effects of the drug by both routes of administration pose some hazards for ambulatory patients particularly at the start of continued therapy or on discharge after outpatient surgery. It is interesting that despite the results of a recent study [4] which show that the public attach great importance to warnings and "bad news" about diazepam, neither the Physician's Desk Reference (PDR) [21], the most frequently used source of drug information for physicians in the United States, nor the two standard textbooks on benzodiazepines [7,11] mention memory and cognitive impairment as side effects from the action of the drug about which patients should be cautioned. Decrement in such functions is in many situations as important as impairment in operating machinery or driving a motor vehicle, situations about which physicians and patients are warned. People whose jobs require constant learning would be particularly vulnerable to the action of the drug.

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