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Differential CNS Effects of Diazepam in Elderly Adults[1]

A. M. NIKAIDO, E. H. ELLINWOOD, JR.,
D. G. HEATHERLY AND D. DUBOW

Behavioral Neuropharmacology Section, Department of Psychiatry, Box 3870
Duke University Medical Center, Durham, NC 27710

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NIKAIDO, A. M., E. H. ELLINWOOD, JR., D. G. HEATHERLY AND D. DUBOW. *Differential CNS effects of diazepam in elderly adults.* PHARMACOL BIOCHEM BEHAV 27(2) 273–281, 1987.—The present study examines the effects of 0.07, 0.14 and 0.21 mg/kg of diazepam on the performance of several cognitive and neuromotor tasks, including wheel tracking, digit symbol substitution and standing steadiness. The drug or placebo was administered at 3-week intervals to healthy elderly men (N=8) and women (N=8). Both medium and high doses significantly impaired performance on the cognitive tasks, whereas only the latter dose induced similar impairment effects on the neuromotor tasks. Wheel tracking and standing steadiness displayed rapid onset and offset of the drug effect, while acute tolerance developed at a considerably slower rate on the digit symbol substitution tasks. Specifically, the subjects continued to show poorer cognitive performance for over 3 hours after dosing, but were no longer impaired on the basically neuromotor skills at 3 hours.

Diazepam Elderly adults Pharmacodynamics Neuromotor skills Cognitive tasks

ALTHOUGH diazepam (Valium) is used frequently by the elderly, there exists only a limited amount of information on the time course of the behavioral effects of acute doses of diazepam for this age group and on the relationship of drug plasma concentration to pharmacologic effect. Previous studies have reported increased drug sensitivity with age in healthy [24, 25, 30] and clinical [1, 3, 27] populations and little or no correlation between drug induced impairment and plasma levels of diazepam, desmethyldiazepam or both combined [24,30].

A more systematic examination of the nature of the diazepam effect on the performance of tasks involving different central nervous system (CNS) processes may contribute significantly to our understanding of the benzodiazepine pharmacodynamic mechanisms in the elderly. The findings from studies with young adults indicate that: (1) diazepam slows their reaction times on simple repetitive motor acts [32] and on tasks with motor and cognitive components [13, 18, 20]; (2) there is a greater drug effect in circumstances of low task demands and monotony than in either challenging and stimulating situations or those involving well-learned higher mental capacities [21,32]; and (3) diazepam impairs decision making performance [20] and blocks the acquisition of new information and skills on learning and memory tasks [10–14, 23, 32].

The present study describes the differential effect of diazepam on the performance of healthy elderly adults on various neuromotor and cognitive tasks and examines the relationship of impairment to drug serum concentration. Three dose levels were administered and sex differences in the drug effect were investigated. Unlike most earlier experiments, subjects were trained to a plateau level of performance on the tasks to remove a major portion of the contribution of learning and practice effects to performance during the test sessions and consequently to reduce inter- and intra-subject variability in the observed drug effect. This procedure also allows the examination of the diazepam effect on well-learned, complex neuromotor-cognitive abilities. Task performance was measured more frequently over a longer period of time than in previous studies to provide a more detailed description of the time course of the drug effect.

METHOD

Subjects

Eight men (mean age=69.0 years, SD=±5.95) and eight women (mean age=68.25 years, SD=±2.82) participated in the present study. The ages of the males and females did not differ significantly. Physical and psychiatric assessment, blood test, including chemistry profile (with hepatic profile) and complete blood count, routine urinalysis and electrocardiogram were conducted to screen for serious medical or psychological disorders and to evaluate liver function. All subjects had no serious physical or psychiatric problems and were not taking CNS active medications. The purpose and procedures of the study were explained to each subject and written informed consent was obtained.

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Tasks

The experimental chamber, apparatus, and the subcritical tracking (SCT), standing steadiness and digit symbol substitution (DSS) tasks have been described in prior reports [7–9]. Testing was conducted in a quiet room which was darkened for all tasks, except for the sway task with eyes open or closed.

Continuous subcritical tracking. The subject was shown a 3 cm wide vertical bar which moved laterally across a 98×128 cm video screen and instructed to maintain the bar in the center of the screen for 3 min by operating a car steering wheel. The first 30 sec was an adaptation ("easy") phase during which the task started at a relatively easy lambda or difficulty level and became gradually harder. The task then remained at the most difficult level for 150 sec ("hard" phase). The position of the bar on the screen was measured at a rate of 60 samples per sec and stored as root mean squared (RMS) units. For both easy and hard phases the mean of the RMS deviations was calculated. A square root transformation of the RMS mean deviation was computed and used as the dependent measure for this task.

Standing steadiness. The sway table consisted of a 46×46×1 cm steel platform mounted on steel bars 6 cm above the floor. A pair of strain gauges was attached to each of four steel bars; the bars were positioned at right angles to each other and divided the top surface of the steel platform into four equal quadrants. A second steel platform, 46×46×1 cm, was placed over the strain gauges. An 11×18.5×1 cm steel board and tape marks were located in the center of the top platform as a guide for the placement of the subject's feet. The strain gauges were used to transduce lateral and anterior-posterior movements into varying voltages which were digitized and analyzed using Fast Fourier transformations.

On two of the sway tasks the subject stood erect on the sway table with his or her arms at his or her sides for 30 sec and either looked at a fixed point in front of the subject or closed both eyes. An overall measure of sway was obtained by summing the power scores of all frequencies below 2.5 Hz in both directions and calculating the square root of this sum.

For the third sway task the subject stood still on the sway table while his or her center of balance was determined during a 5-sec calibration period. A circle, 60 cm in diameter, was then drawn on the display screen. Located in the center of the circle, a "+" symbol represented the center of balance for the subject. The current position of the subject in relation to this center of balance and his or her positions for the previous 1 sec were indicated by a series of dots. The subject attempted to minimize swaying for 60 sec by keeping the dots as close as possible to the "+". Anterior-posterior and lateral motions were measured and the mean distance from center was computed.

Digit symbol substitution. This task is a computerized version of the DSS subtest from the Wechsler Adult Intelligence Scale-Revised [31]. The DSS code table of nine numerals (1 to 9) and symbols was projected on the screen during the entire task. A symbol appeared below the table and remained on the screen until the subject pressed on a 9-digit keypad the number located above that symbol on the table. Numbers and symbols were randomly paired at the beginning of the task which consisted of 12 random presentations of each symbol. The subject was instructed to respond quickly and accurately. The response measures for the total sequence of 108 trials and for the first 30 (F30) and last 30 (L30) responses included the total number of correct responses (NC) and the average reaction time (RT) for right responses only.

Digit symbol substitution memory. The procedure and analysis of the digit symbol substitution memory (DSSM) task were identical to the DSS task, except for the following modifications. The DSS part of the task was divided into four quartiles with 3 presentations of each symbol per quartile. At the end of each quartile, the code table was erased and individual symbols were displayed on the screen. The subject was asked to recall and press on the keypad the number paired with the symbol in the current code table. This cued recall test was self-paced and accuracy was stressed. The dependent measures consisted of those described for the DSS task and the NC for each recall test.

Keypad reaction time. A number from 1 to 9 was displayed in the center of the screen and the subject pressed the same number on the keypad. One hundred randomly selected digits were presented during the keypad reaction time (KRT) task. The stimulus remained on the screen until a response was recorded. The subjects were instructed to respond as quickly and accurately as possible. The response measures were the same as those for the DSS task.

Procedure

The subjects were trained on the tasks during four or more 2-hr sessions until no substantial improvement in the scores was observed. Placebo and diazepam were administered according to a crossover Latin Square design balanced for dose order. The Duke University Medical Center Pharmacy calculated and weighed out in powdered form three doses of diazepam for each subject on the basis of 0.07, 0.14 and 0.21 mg/kg of body weight or approximately 5, 10 and 15 mg, respectively, for a standard 70 kg person.

Four test sessions were scheduled for each subject at 3-week intervals to insure complete washout of any residual drug. Subjects fasted for at least 2.5 hr prior to ingesting the drug and consumed no alcohol or recreational drugs within the previous 24 hr. Using a double-blind procedure, a single acute dose of placebo or diazepam was suspended in a starch lactose solution and given PO between 1:30 p.m. and 2 p.m. Subjects were tested prior to and at various intervals for 67 hr following drug administration (see Table 1). A 7 ml venous blood sample was drawn periodically from an obturated indwelling catheter in the subject's forearm.

Diazepam and N-desmethyldiazepam serum levels were determined after extraction by electron-capture detection gas chromatography [15]. Since the metabolite has been shown to be one-half as potent per unit weight as diazepam [22], total drug concentration was represented as diazepam plus one-half of N-desmethyldiazepam levels. Previous studies [4,16] have reported that the elimination half-life of diazepam can be as long as 100 hr in the elderly. Since blood samples in the present study were only collected for 67 hr after drug ingestion, there was not sufficient data to conduct any accurate pharmacokinetic analyses.

Analysis

Repeated measures analysis of covariance with the predrug score as the covariate and time of testing as the repeated factor was used to evaluate the effects of dose, sex and relative time of testing on task performance. Predrug scores were not significantly correlated with dose level. The

TABLE 1
STUDY PROTOCOL

Time	Procedure
−25 min	Subcritical tracking (SCT)
	Digit symbol substitution (DSS)
	Catheter insertion
	Blood sample
	All tasks
0 min	Drug administration
+5 min	SCT
+10 min	SCT
+15 min	SCT
+20 min	Blood sample
	Sway with eyes open, DSS, SCT
+30 min	Blood sample
+40 min	SCT
+45 min	Blood sample
+60 min	Blood sample
	All tasks
+90 min	Blood sample
+95 min	SCT
	Rest period (subject may walk around)
+120 min	Blood sample
	All tasks
+180 min	Blood sample
	All tasks
	Meal (sandwich and uncaffeinated soda)
+240 min	Blood sample
	All tasks
+9 hr	Blood sample
+19 hr	Sway with eyes open, DSS, SCT
	Blood sample
+27 hr	Blood sample
+43 hr	Sway with eyes open, DSS, SCT
	Blood sample
+67 hr	Sway with eyes open, DSS, SCT
	Blood sample

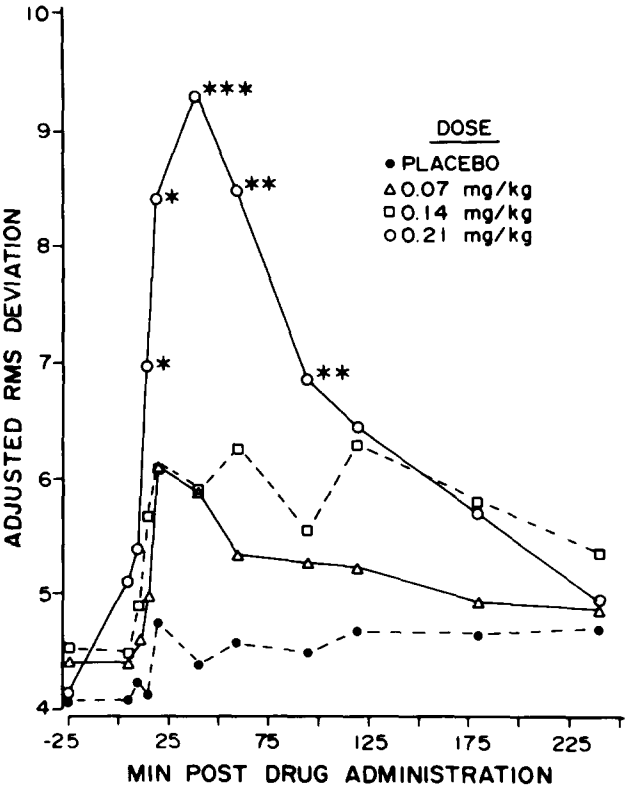

FIG. 1. Impairment on the continuous subcritical tracking task at −25 min (predrug) and at 5, 10, 15, 20, 40, 60, 95, 120, 180 and 240 min post drug administration. The treatment conditions were placebo (●), and 0.07 (△), 0.14 (□) and 0.21 (○) mg/kg of diazepam. The lines join performance means for successive testing time points. The dependent measure for the tracking task was the square root transformation of the root mean squared (RMS) deviations of the tracking bar from the center of the screen. *, **, *** represent $p<0.01$, $p<0.001$, and $p<0.0001$ levels of significance, respectively, for the t-tests and indicate significant differences between placebo and each of the diazepam doses.

Huynh-Feldt correction [19] was applied to the probability levels of the F values. Due to the number of mean comparisons, an alpha level of 0.01 was used to determine the significance of t-tests comparing performance at each of the three doses with that of the placebo condition. t-Tests were conducted on means adjusted for the predrug score. The actual scores for each performance task were correlated with the observed total drug serum levels to determine the degree of association between drug concentration and the behavioral effects of diazepam.

RESULTS

Performance for all of the tasks had returned to the predrug baseline level at 19, 43 and 67 hr after drug administration and no significant residual drug effects were found at these testing times. Consequently, in order to present the data more clearly, the results in the figures will include only the initial 4 hr of the test sessions.

Continuous Subcritical Tracking

There was a significant interaction between dose and time of measurement for performance at the most difficult level of the SCT task, $F(36,564)=3.01$, $p<0.0002$. As shown in Fig. 1, performance during the hard phase was significantly impaired at the highest dose, but not at the lower doses. The onset of the diazepam effect was rapid and maximum impairment was observed at 40 minutes. The elderly subjects demonstrated an equally fast recovery from impairment and by 2 hr the mean tracking deviation scores for the 15 mg dose no longer differed significantly from the mean placebo scores.

The interaction between dose and time of testing approached significance for the easy version of the SCT task, $F(36,564)=1.46$, $p<0.08$, and the high dose produced a similar time course of impairment as for the hard phase; that is, a quick increase in impairment followed by rapid improvement in performance. However, the magnitude and duration of the

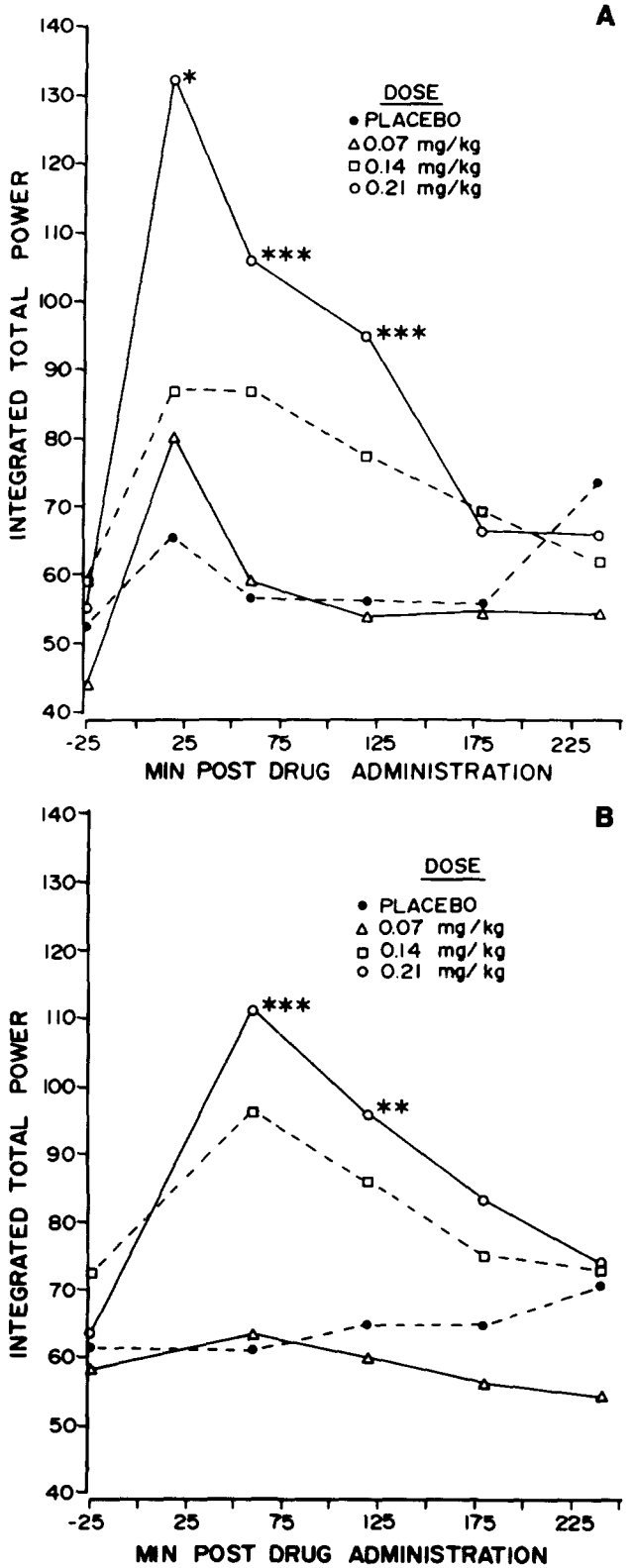

FIG. 2. Impairment on the standing steadiness task with eyes open (A) and eyes closed (B) for the diazepam doses. Performance was assessed at −25, 20, 60, 120, 180 and 240 min for the eyes open condition and at −25, 60, 120, 180 and 240 min for the eyes closed condition. Sway was measured as the sum of the power scores of all frequencies below 2.5 Hz for body movements in the lateral and anterior-posterior directions. The treatment conditions, curves, symbols and significance levels are described in Fig. 1.

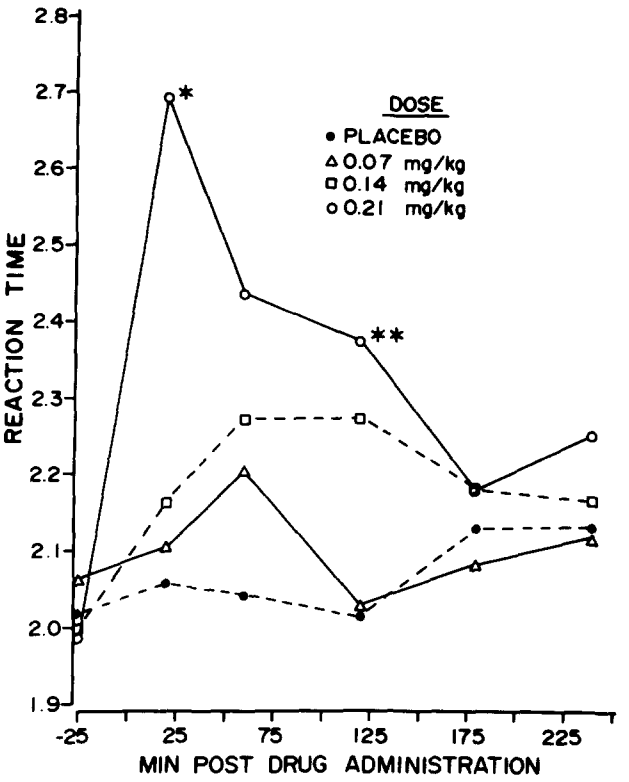

FIG. 3. Impairment on the digit symbol substitution task for the diazepam doses at −25, 20, 60, 120, 180 and 240 min. The response measure for the individual subjects was the average reaction time for the correct responses made during the first 30 trials of the task. The treatment conditions, curves, symbols and significance levels are explained in Fig. 1.

effect of 15 mg on the easy tracking was less than that of the effect on the hard portion. Specifically, diazepam significantly ($p<0.01$) impaired performance only at 40 min after drug ingestion during the initial adaptation phase and the observed maximum easy SCT score was 8.45. The 5 and 10 mg doses did not significantly alter the easy SCT scores.

Standing Steadiness

Dose interacted significantly with time of assessment for the eyes open, $F(21,385)=3.21$, $p<0.0001$, eyes closed, $F(9,165)=1.97$, $p<0.05$, and visual feedback, $F(9,165)=2.03$, $p<0.05$, versions of the sway task. As for SCT, only the 15 mg dose induced significant impairment on all three sway tasks. The power scores for the eyes open and eyes closed tests are presented in Figs. 2A and 2B, respectively. For both, maximum impairment was observed during the first hour after drug administration at the time of the earliest postdrug assessment, and the effects of diazepam on postural steadiness lasted at least until 2 hours following drug ingestion. Comparison of the tasks in Fig. 2 further suggests that the subjects were slightly more unsteady with their eyes closed.

In addition, there are indications that providing visual feedback of the standing positions reduced the degree of swaying in both the intoxicated and nonintoxicated conditions, especially for the males. First, while the time courses of the drug effect were similar for the three standing steadiness tasks, performance on the sway task with visual feed-

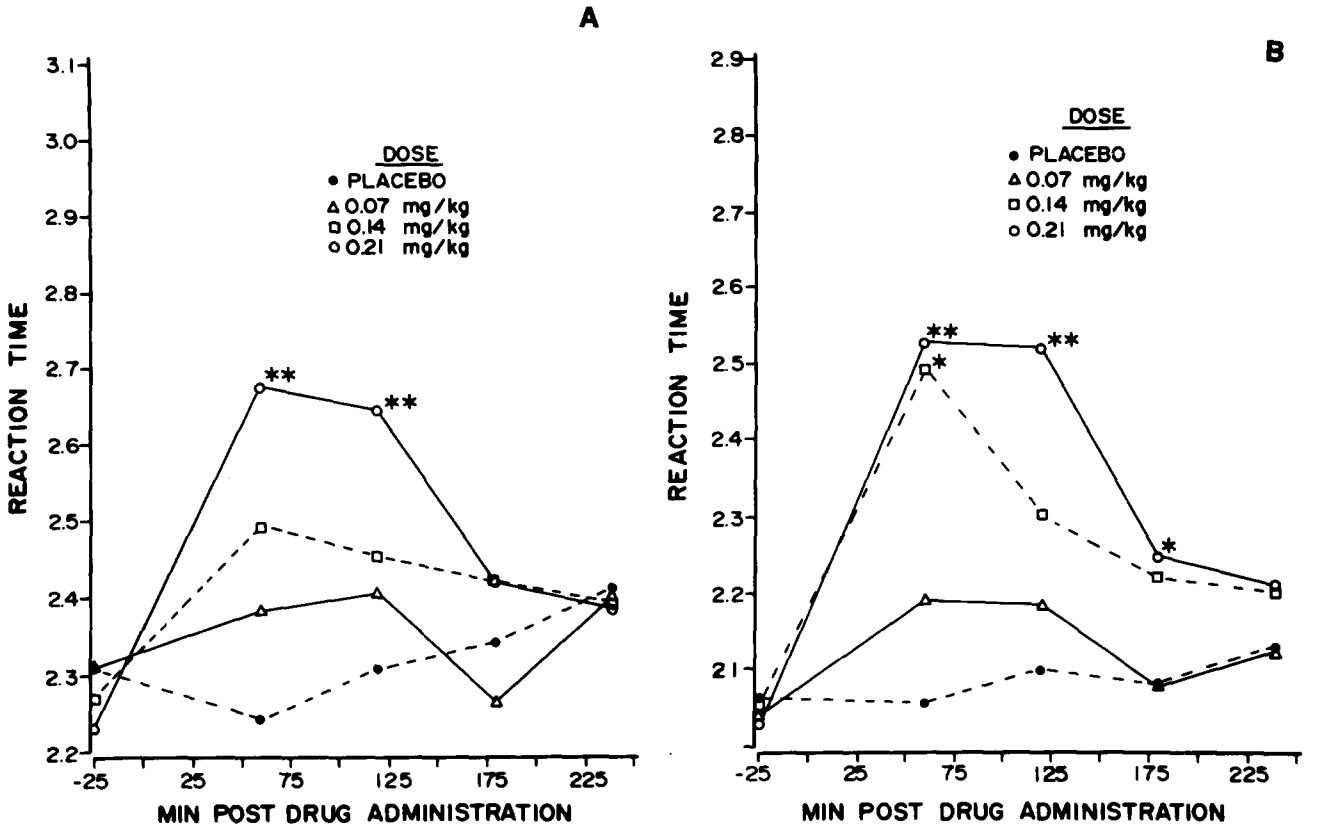

FIG. 4. Impairment on digit symbol substitution memory task for the diazepam doses at −25, 60, 120, 180 and 240 min. The mean reaction time for correct responses during the first 30 and all 108 trials of the test is shown in A and B, respectively. The treatment conditions, curves, symbols and significance levels are the same as in Fig. 1.

back was significantly impaired at just 2 hr post drug administration. Thus, of all the standing steadiness measures the visual feedback task was the least sensitive to diazepam. Second, in general, the men tended to be more unsteady than the women for the eyes open, $F(1,54)=4.21$, $p<0.05$, and eyes closed, $F(1,54)=4.32$, $p<0.05$, situations but not for the visual feedback task. This sex difference in ataxia was also present in the undrugged condition; the mean sway scores for the men were 20% to 60% higher than those for the women on the predrug evaluations of the four test sessions and on the postdrug assessments of the placebo treatment.

Digit Symbol Substitution

The dose effect was significant for total NC, $F(3,54)=2.83$, $p<0.05$, and total average RT, $F(3,54)=2.99$, $p<0.04$. The overall mean scores for the 4-hour test session showed that the subjects committed significantly more errors and responded more slowly after the medium ($p<0.05$) and high ($p<0.0001$) doses than after the placebo condition. In addition, there was a significant interaction between dose and testing time for the average RT of the F30 responses, $F(21,385)=2.22$, $p<0.03$. t-Tests indicated that the responses of the subjects were significantly delayed only after the high dose at 20 min ($p<0.05$) and at 2 hr ($p<0.01$) following drug administration (Fig. 3). Since the mean RT of the L30 trials was generally faster than the mean RT of the F30 trials for the placebo condition at all testing time points, the failure to detect a significant drug effect during the final segment of the DSS task was not due to a ceiling effect on the L30 performance.

Digit Symbol Substitution Memory

Dose level was a significant factor for the F30 NC, $F(3,54)=3.02$, $p<0.04$ and total NC, $F(3,54)=4.91$, $p<0.005$, of the DSS portion of the DSSM test. Mean total NC for the 4-hour test day was significantly decreased by the 10 ($p<0.05$) and 15 ($p<0.0001$) mg doses, while the mean NC of the F30 responses were lower only after the high dose ($p<0.001$). A significant interaction between dose and sex was also observed for the L30 NC, $F(3,54)=3.15$, $p<0.04$; the older males, but not the females, made significantly more errors during the 4 hours of testing after the medium ($p<0.01$) and high ($p<0.0001$) doses than after the placebo treatment.

A slowing of the response rate during the DSS portion of the DSSM task was reflected in the significant interaction between dose and time of testing for the F30, $F(9,165)=2.55$, $p<0.01$, and total, $F(9,165)=2.6$, $p<0.02$, average RT. As depicted in Figs. 4A and 4B, there was a dose-related increase in RT and the drug effect lasted from 1 to 3 hr after the medium and high doses. A notable phenomenon of both figures is the maintenance of stable, nearly equivalent levels of impairment from 1 to 2 hr after administration of the high dose. This plateau in the drug effect contrasts sharply with the linear decline in impairment observed at the same time intervals for the SCT and sway tasks.

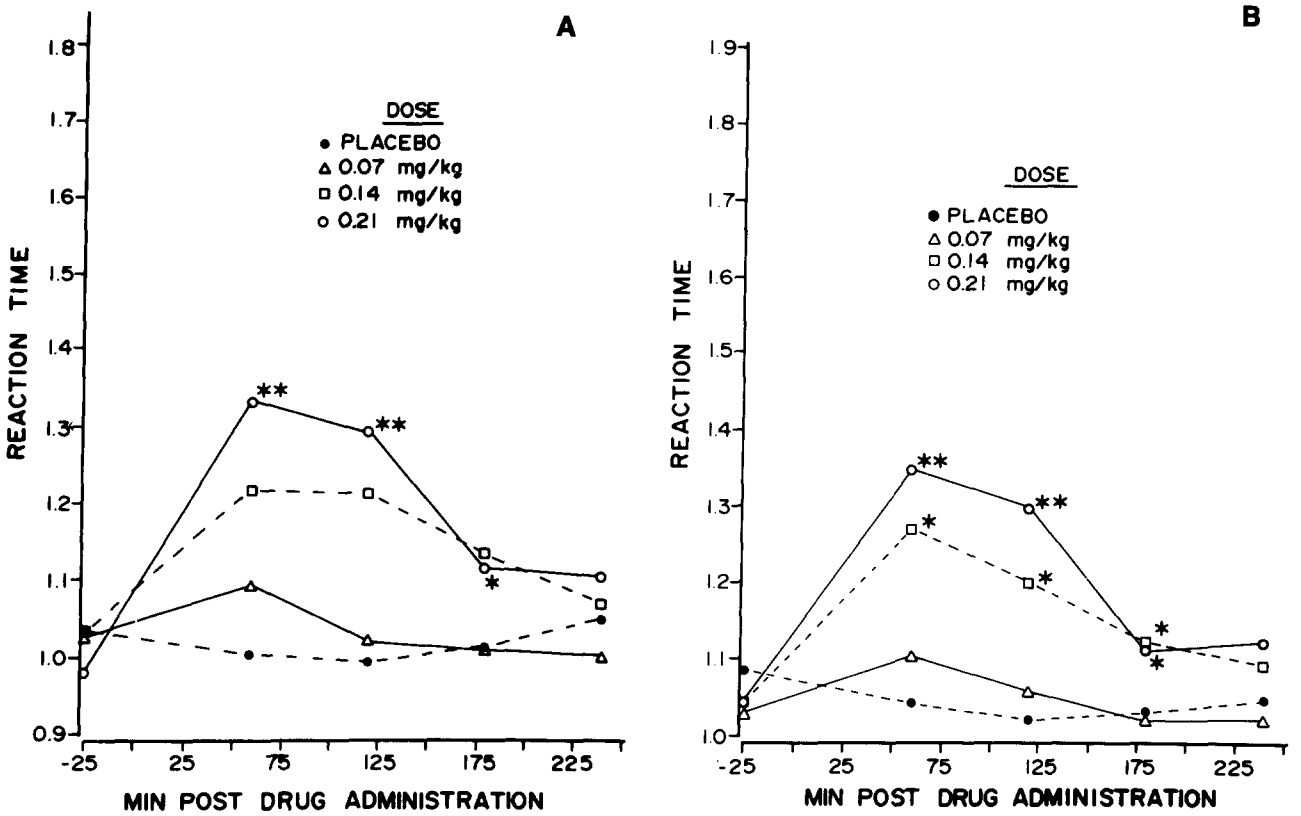

FIG. 5. Impairment for the keypad reaction time task for the diazepam doses at −25, 60, 120, 180 and 240 min. The mean reaction time for correct responses during the last 30 and all 108 trials of the test is shown in A and B, respectively. The treatment conditions, curves, symbols and significance levels are presented in Fig. 1.

The curves in Figs. 4A and 4B further demonstrate that the F30 response times for the placebo and drug conditions were prolonged in comparison to the total RT. Moreover, the mean RT score for the L30 trials of the placebo condition was also consistently faster than for the F30 trials and indicated that a ceiling effect could not account for the lack of a significant drug effect on the L30 RT.

For the cued recall tests, dose had a significant effect on NC for the third, $F(3,54)=3.07$, $p<0.04$, and fourth, $F(3,54)=4.18$, $p<0.01$, quartiles and approached significance for the second quartile, $F(3,54)=2.02$, $p=0.12$. Compared to performance during the placebo treatment, less number-symbol pairs were recalled correctly during the entire test session after the high dose for the second ($p<0.01$) and third ($p<0.0001$) quartile recall tests and after both medium ($p<0.001$) and high ($p<0.0001$) doses for the final recall test. The mean NC for the first, second, third and fourth quartiles of the placebo test session were 3.962, 5.312, 6.175 and 6.788, respectively. The particularly low value for the first quartile recall test suggests that a ceiling effect may have contributed to the nonsignificant results for the NC of the initial memory test.

Keypad Reaction Time

The interaction between dose and time of testing was significant for the L30, $F(9,165)=2.31$, $p<0.03$, and total, $F(9,165)=2.44$, $p<0.03$, average RT. The two higher doses increased the response times of the elderly subjects for as long as 3 hours after drug ingestion (Figs. 5A and 5B). Since the F30 RT of the KRT task was slower than the L30 RT, a ceiling effect may explain the absence of a significant drug effect on the initial segment of the task.

The L30 and total NC for the 4 hr of testing was significantly lower after the medium ($p<0.05$) and high ($p<0.0001$) doses than after the placebo treatment. The data, however, indicate that the subjects were equally or slightly more accurate for the F30 responses than they were for the L30 trials during the drug treatment sessions. Consequently, diazepam appeared to induce a greater effect on the accuracy of performance on the later than the earlier trials of this task.

Drug Concentration

Since there were no significant sex differences for the diazepam, N-desmethyldiazepam or total drug serum concentration, the measures for the males and females were combined and analyzed. The time course for the observed total drug concentration, consisting of diazepam and one-half of the N-desmethyldiazepam levels, is shown for each dose in Fig. 6. There was a dose-related increase in serum levels and the observed time to maximum drug concentration (TMAX) was 45 min following drug administration for the 5 and 15 mg doses and 1 hr after dosing for 10 mg. The TMAX in the present experiment generally agreed with previous studies that have reported a diazepam TMAX, ranging from 0.88 to 1.4 hr, for elderly subjects [4,28].

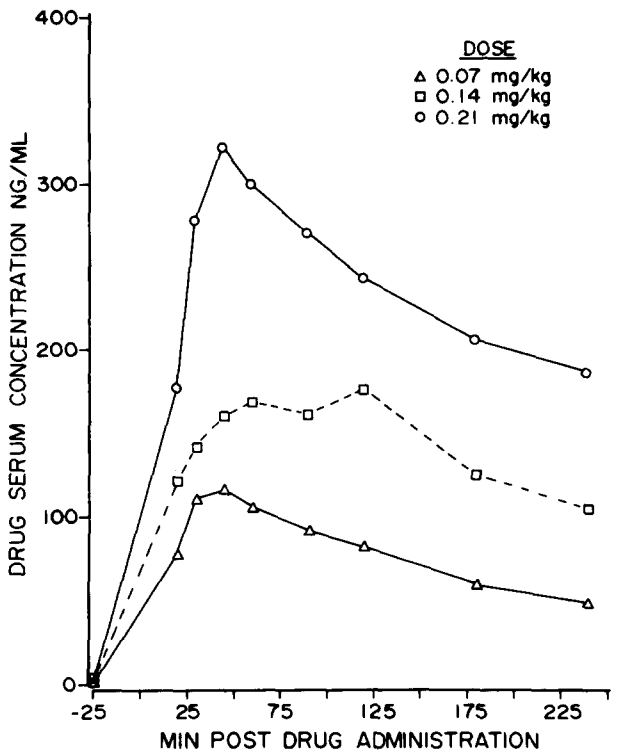

FIG. 6. Drug serum concentration values for the three diazepam doses, 0.07 (△), 0.14 (□), and 0.21 (○) mg/kg, at −25, 20, 30, 45, 60, 90, 120, 180 and 240 min. The means of the actual drug levels obtained for consecutive sampling intervals are represented for each dose. The symbols and curves are explained in Fig. 1.

The SCT, sway and RT performance scores correlated significantly and positively with the observed total drug concentration (r=0.18 to 0.40, $p<0.01$). The NC measures were negatively related to the serum levels (r=−0.19 to −0.34, $p<0.01$). The strongest association between the performance and drug values was observed for the SCT (r=0.40), sway with eyes open (r=0.38) and eyes closed (r=0.36) tasks and DSSM total NC (r=−0.34).

DISCUSSION

The elderly adults demonstrated distinctive patterns of sensitivity to the effects of diazepam on the performance of tasks involving different CNS processes. The neuromotor tasks (SCT and sway) assessed primarily motor coordination skills, and the cognitive tasks (DSSM and KRT) were characterized by the integration of cognitive and motor functions, including learning, memory, perceptual-motor and complex reaction-time capacities. Although diazepam induced substantial impairment on both types of tasks, the results indicated that the cognitive tasks were relatively more sensitive to the effects of the drug. Specifically, DSSM and KRT performance was significantly impaired by both 10 and 15 mg doses, while impairment on the SCT and sway tasks was noted only after 15 mg.

Of greater significance is the finding that while the time course for the onset of impairment was similar for all of the tasks, duration of impairment for the various tasks differed. The SCT and sway tasks displayed a faster offset of the drug effect and were no longer impaired significantly by 2 and 3 hours after dosing, respectively. In contrast, recovery from impairment on the DSSM and KRT tasks did not occur until 4 hr. Swift and Stevenson [30] also reported a longer period of impairment for the DSS than for postural sway tasks in elderly subjects at the 10 mg dose.

The comparison between the time courses of performance impairment (Figs. 1 to 5) and drug concentration (Fig. 6) indicates (1) a closer correspondence between the pharmacokinetics and pharmacologic activity of diazepam during the impairment onset phase than during the effect offset phase and (2) the development of acute tolerance following peak impairment. The maximum drug effect after administration of the 15 mg dose was observed at 40 min for SCT, the most frequently evaluated task, and similarly within 1 hr for the other tasks at either the 10 or 15 mg doses. The appearance of the initial peak performance impairment at 1 hr or earlier corresponds to the TMAX found for diazepam blood concentration in the present and other oral dosing experiments [4,28]. These findings suggest that diazepam absorption pharmacokinetics is the primary determinant of how quickly the behavioral performance of elderly individuals becomes impaired.

Pharmacokinetics alone, however, do not completely explain either the phenomenon of acute tolerance or the differences in the duration of the drug effect for the various tasks. Whereas mean serum drug level had declined only by about one-third of the maximum concentration at 4 hr for the 15 mg dose, performance on all of the tasks returned close to predrug levels during the same period. Acute tolerance developed more quickly for the SCT and sway than for the cognitive tasks. Furthermore, during the first 2 hr after drug administration the same pharmacokinetic processes could not be responsible for the relatively rapid rate of recovery for the SCT task as well as the sustained levels of impairment (plateau phase) for the DSSM and KRT tasks. Thus, the data raise important questions concerning the possibility of variable responsivity to diazepam in the CNS areas involved in the different tasks.

In addition to pharmacokinetic processes, other potential mechanisms that may contribute to the findings of the present study include receptor kinetics, adaptation and affinity. The pharmacological and clinical potencies of benzodiazepines have been shown to correlate significantly with benzodiazepine receptor affinity [2], suggesting that this receptor is the site of clinical action for these compounds. Recent studies have further hypothesized that two receptor subtypes, BZ_1 and BZ_2, are differentially distributed in the cortical areas [2, 5, 29]. As yet, the exact relationship between the BZ_1 and BZ_2 receptors and the behavioral effects of benzodiazepines has not been determined. However, other research has shown that the aging process may actually alter the response of the receptor subtypes to diazepam [26] and raises the question of the role of such changes in the sensitivity of elderly individuals to the benzodiazepines.

The effect of diazepam on learning was assessed by the DSS and DSSM tasks which required the learning of a new code table or novel number-symbol pairings for each presentation of the task. The presence of practice or learning effects was confirmed by the faster RT of the L30 trials of these tasks and by the improvement in NC for the recall tests of the four quartiles. As in previous studies with young subjects [13,32], diazepam had a significant effect on performance measures which demonstrated practice effects, that is, the F30 RT of the DSS and DSS segment of the DSSM task and memory NC.

Alternatively, a major portion of the data indicated that diazepam caused substantial and rapid performance decrement relative to the predrug level for well-learned capabilities. The presence of minimal practice effects during the 4-hr test session for the placebo condition showed that the subjects were well-trained on all of the tasks (Figs. 1 to 5). Although the SCT, sway and KRT tasks did not require the learning of new skills or information, performance on all of these tasks were significantly impaired by the drug. Of particular interest is the observation that unlike the DSS and DSSM tasks diazepam affected the RT and NC of the L30 but not the F30 KRT trials. The most likely explanation is that there was a fatigue effect for the KRT task.

The lack of substantial practice effects between the testing time points of each treatment session is an important distinction between the present and earlier experiments [24,25]. This difference in the nature of the tasks may explain the failure of the lowest 5 mg dose to impair the performance of the elderly subjects in this study, while Pomara *et al.* [24] reported impairment of memory and reaction time tasks by 2.5 and 5.0 mg of diazepam.

The results for the three sway tasks present evidence of a role for the visual system in maintaining postural balance. The data indicate that (1) the sway task with visual feedback was less impaired than the eyes open or closed conditions and (2) providing visual feedback helped the elderly men to decrease swaying.

There were no significant sex differences for the effect of diazepam on all of the tasks, except for L30 NC of the DSSM task. The lack of a differential drug effect for the elderly men and women agrees with the results of earlier studies [3,24]. Finally, while the present study was unable to address directly the question of age differences in the behavioral effects of diazepam, the elderly adults in this experiment demonstrated similar patterns of reactivity to diazepam as shown in other studies with young adults [6, 8, 10–13]. Further research with young and elderly subjects needs to be conducted to specify in greater detail the nature of the influence of age on sensitivity to the benzodiazepines and the interactions between the aging process, sex and drug sensitivity.

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