Differential effects of zolpidem, triazolam, and diazepam on performance in a radial maze task

JUNE J. PILCHER and G. RUFUS SESSIONS
Walter Reed Army Institute of Research, Washington, D.C.

The effects of zolpidem, triazolam, and diazepam on performance in an eight-arm radial maze task were studied in the rat. Errors were based on arm entries as well as nose pokes in a food trough and were summed across the number of correct choices remaining. As measures of motivation, number of pellets retrieved, number of arm entries, total time in maze, and time from arm entry to nose poke were recorded. Triazolam and diazepam resulted in a greater performance decrement than did zolpidem. Furthermore, triazolam and diazepam appeared to have a sedative effect on the animals that did not affect the motor control needed to complete the task. The present results suggest that the BZ-1-specific hypnotic, zolpidem, did not produce sedative or performance effects as profound as those produced by the nonselective benzodiazepines, triazolam and diazepam.

The benzodiazepines have been used successfully as major anxiolytics and sedatives since their introduction in the 1950s. However, many of the benzodiazepines and similar hypnotics have a memory-impairing or amnesic effect (Cole, 1986; Ghoneim, Hinrichs, & Mewaldt, 1984; Lister, 1985; Romney & Angus, 1984; Smith, 1984; Weingartner, Hommer, Lister, Thompson, & Wolkowitz, 1992) at doses that also produce the desired anxiolytic and sedative effects (Kalynchuk & Beck, 1992). Although it is unlikely that the anxiolytic effects of the benzodiazepines could result in memory deficits (Kalynchuk & Beck, 1992; McMillan, 1982; Nicholson & Wright, 1974), it is possible that the amnesic effects induced by the benzodiazepines could be secondary to benzodiazepine-induced sedation, in that benzodiazepine administration in animals and humans has resulted in motor, as well as attentional, deficits that correlate with the detriments in performance (see, e.g., Poling, Pickler, Van de Polder, & Clark, 1986; Preston et al., 1988; Willner & Birbeck, 1986). One means of more thoroughly examining the sedative versus the memory effects of the benzodiazepines is to use animal models that allow for measures of motor behavior, as well as measures of learning and memory. One such model is the radial arm maze.

Although the radial arm maze is a commonly used method for testing spatial learning and memory in rodents, relatively few studies have used this model to examine the effects of the benzodiazepines on behavior, and those studies that have used the radial arm maze have reported mixed results. For example, although some studies have indicated that chlordiazepoxide impairs choice accuracy and increases time to maze completion (Hodges & Green, 1986; Willner & Birbeck, 1986), other studies have not (Hiraga & Iwasaki, 1984). In addition, some researchers have used the radial arm maze to examine behavior and have reported a reduction in variability in behavior due to diazepam administration (Beck & Loh, 1990; Loh & Beck, 1989). These results indicate that the benzodiazepines may impair the ability of the animal to complete the radial maze task, as well as their ability to complete the task without error.

Studies using other animal models of learning and memory have also suggested that the benzodiazepines may impair task performance. For example, diazepam has been shown to impair acquisition of the Morris open pool water maze, but not performance on the previously learned maze (McNamara & Skelton, 1991). In a water maze that involves a traditional maze task with alleyways and doorways, diazepam has been shown to result in a greater increase in the time needed and the number of errors made when completing three consecutive trials at a new water maze task than when completing a previously learned water maze task (Kant, 1993). In a related study, completion of a previously learned water maze task was not affected by either diazepam or triazolam (Kant, Wylie, Vasilakis, & Ghosh, 1996). However, diazepam was found to increase the number of errors committed, and triazolam was found to increase the time needed and the number of errors made while completing new water maze configurations. These data suggest that the benzodiazepines affect acquisition more readily than memory of different types of maze tasks.

An additional means of differentiating between the performance and sedative effects of the benzodiazepines is to examine whether these effects are dependent on how the...
drugs are utilized by the nervous system. The benzodiazepines produce their general effects of sedation, amnesia, and muscle relaxation by acting on specific benzodiazepine sites associated with the GABA<sub>A</sub> receptors (Möller & Okada, 1977). Two types of benzodiazepine receptors, known as BZ-1 (ω₁) and BZ-2 (ω₂), have been documented (Langer & Arbilla, 1988; Sieghart & Schuster, 1984; Squires et al., 1979). However, not all hypnotics act with equal affinity on the two receptor subtypes. Classical benzodiazepines, such as diazepam and triazolam, use both BZ-1 and BZ-2 receptors with equal affinity (Griebel, Sanger, & Perrault, 1996). In contrast, the imidazopyridine hypnotic, zolpidem, binds with high affinity to the BZ-1 receptor subtype only (Lüddens, Korpi, & Seeburg, 1995; Sanger et al., 1994).

On the basis, in part, of findings of receptor selectivity by different hypnotics, researchers have theorized that the behavioral profile of the benzodiazepines and other hypnotics may be related to receptor subtype specificity (Sanger et al., 1994). Some support for this hypothesis has been found. For example, zolpidem administration decreased exploration at lower doses than it did general muscle relaxation, whereas triazolam specifically affected muscle strength (Zivkovic, Perrault, & Sanger, 1992). Another study concluded that zolpidem seemed to have a preferential sedative effect that may interfere less with performance than other hypnotics, whereas triazolam may be more active in creating amnestic effects than in creating sedative effects (Sanger, Joly, & Zivkovic, 1986). More recently, Griebel et al. (1996) concluded that both nonspecific benzodiazepines (e.g., diazepam) and BZ-1–selective hypnotics (e.g., zolpidem) resulted in less horizontal motor activity, with the BZ-1–selective hypnotics resulting in generally smaller reductions in motor behavior than did the nonspecific benzodiazepines. However, in normal healthy adults, both triazolam and zolpidem administration produce memory deficits (Balkin, O'Donnell, Wesensten, McCann, & Belenkky, 1992; Roehrs, Merlotti, Zorick, & Roth, 1994). Therefore, although some studies have supported a link between the amnesic and sedative effects of the benzodiazepines and other hypnotics, the differential effects of the nonspecific benzodiazepines and the BZ-1–selective hypnotics on memory and motor activity are not clear.

The purpose of the present study was to use the traditional radial arm maze task to study the effects of two non–specific benzodiazepines, triazolam and diazepam, and of a BZ-1–selective hypnotic, zolpidem, on performance and motor activity in the rat. We have developed a scoring paradigm that allows us to document performance, as well as several measures of motivation and motor activity, using the radial arm maze (Pilcher, Sessions, & McBride, 1997). Errors are defined as either arm entry errors (defined as breaking a vertical plane 15 cm inside the arm entrance) or nose poke errors (defined as breaking a vertical plane inside the food trough positioned at the end of each arm). Because arm entry errors are easier to make than nose poke errors, we expected more arm entry errors than nose poke errors to be committed. As an additional measure of performance, all errors were summed across each correct choice, permitting us to examine the pattern of errors across correct choices made. The number of errors was expected to increase as the number of correct choices decreased for the benzodiazepines, but less so for zolpidem, reflecting the differential effects of these hypnotics on memory. As measures of motivation and motor activity, we recorded time to maze completion, latency from arm entry to nose poke, total number of food pellets retrieved, and total arm entries. We expected that, if the benzodiazepines and, to a lesser extent, zolpidem resulted in substantial detriments in motor behavior in the radial maze, they would result in an increased time to maze completion, as well as in fewer pellets retrieved and fewer arms entered. Therefore, on the basis of the hypothesis that the BZ-1–selective hypnotic, zolpidem, would result in less pronounced behavioral effects than the benzodiazepines, we expected diazepam and triazolam to result in more errors and less motor activity than zolpidem.

**METHOD**

**Subjects**

Ten male, drug-experienced Sprague–Dawley rats (Zivic Miller Laboratories, Allison Park, PA), approximately 5 months old at the beginning of the experiment, served as subjects. The animals were housed in an air-conditioned colony room in individual acrylic cages with freely available water. The room was illuminated with fluorescent lights maintained under a 12:12-h light:dark cycle, with light onset at 6 a.m. Sufficient food was made available to maintain the animals at approximately 80% of their free-feeding body weights. The animals’ body weights under the partial food deprivation condition ranged from 298 to 385 g across the duration of the experiment.

**Apparatus**

A symmetrical, totally enclosed, eight-arm radial maze was used. The maze was constructed from 6.25-mm polycarbonate plastic and was mounted on stainless steel legs 75 cm above the floor. The arms extended from an octagonal center compartment 51.5 cm in diameter and 12.7 cm high. Each arm was 19.7 cm wide, 61 cm long, and 12.7 cm high. A photocell sensor was positioned 15 cm inside the entrance of each arm. The center of the maze was separated from the arms by guillotine gates that were operated manually by an experimenter approximately 3 m from the radial maze by strings suspended from the ceiling. A photocell-equipped recessed food trough was mounted on the end wall of each arm connected to a food dispenser (Coulbourn Instruments, Allentown, PA). The food dispenser delivered one 45-mg food pellet (Dustless Purified Diet Precision Pellets, BioServ, Frenchtown, PA) when the food trough photocell beam was interrupted. Also mounted on the end wall of each arm was a 1.27-cm miniature stimulus light. Additional details on the construction of the maze have been described previously (Elsmore & McBride, 1994).

The maze was housed in an air-conditioned room and was surrounded on all sides by walls, equipment racks, or office separator panels. The separator panels were made visually distinguishable by a 24.13-cm-high plus sign or triangle attached to the panels. A laboratory computer (PDP 11/73, Digital Equipment Corporation, Nashua, NH) running SKED-11 software (Snapper & Inglis, 1985) was interfaced with each photocell in the maze by Lablink interface modules (Coulbourn Instruments) and was programmed to detect
arm entries, arm exits, and nose pokes into the food troughs and to deliver pellets.

**Procedure**

**Eight-arm radial maze paradigm.** The animals performed the eight-arm maze task 5 days a week (Monday through Friday) between 12:00 and 4:00 p.m. The laboratory computer was programmed to record time and event codes upon interruptions in the photocell receptors inside the arm entrances, indicating an arm entry or exit (beam breaks) or interruptions in the food trough photocell receptors (nose pokes), and to deliver one pellet following the first nose poke in each arm. All the animals were experienced in the maze and had received daily test sessions under the eight-arm radial maze paradigm for several months prior to the onset of the present experiment.

Each animal was placed in the center of the maze with the doors to all the arms closed at the onset of each trial. Approximately 30 sec later, the stimulus lights at the end of each arm were turned on by the computer, indicating the beginning of the trial. The experimenter then raised all the doors and allowed the animal free access to all the arms. After the animal entered an arm, all the arm doors were closed except the door for the arm entered. When the animal exited the arm, that arm door was closed, and all the arm doors remained closed for 5 sec, thus containing the animal in the center of the maze and discouraging patterning behavior. After the 5 sec had elapsed, all the doors were raised, and the animal could select an arm to enter. This pattern was repeated until the animal retrieved a pellet from each arm or until 10 min had elapsed, thus ending the trial. The training procedure for adaptation to the radial maze and the eight-arm radial maze paradigm is described more thoroughly in a previous study (Pilcher et al., 1997).

**Drug sessions.** Drug tests consisted of a drug or vehicle injection (i.p.) 30 min prior to testing on Tuesday and Friday of each week. On Monday, Wednesday, and Thursday of each week, the animals completed the eight-arm radial maze task under nondrug conditions. Drug doses used in the present experiment were based on the doses reported in the literature on studies in which the maximum doses resulted in sedative effects on different types of motor behavior (e.g., Beck & Loh, 1990; Depoortere et al., 1986; File, 1981; Griebel et al., 1996; Kalyanchuk & Beck, 1992; Kant et al., 1996; Massotti et al., 1991). Zolpidem was the first drug tested. Zolpidem was dissolved in distilled water and injected at doses of 0.0, 0.33, 1.0, and 3.0 mg/kg 30 min prior to the beginning of the maze task. Drug dose administration was completed in a counterbalanced fashion, resulting in each animal receiving each drug dose and vehicle condition once. A second replication was completed approximately 2 weeks after the conclusion of the first replication, using the same animals, drug doses, and conditions.

Approximately 1 month after the conclusion of the zolpidem drug testing, the animals were tested with triazolam. Triazolam was suspended in a mixture of 50% polyethylene glycol and 50% distilled water and injected at doses of 0.0, 0.05, 0.1, and 0.2 mg/kg 30 min prior to the onset of the radial maze task. Drug dose administration was completed in a counterbalanced fashion, resulting in each animal receiving each drug dose and vehicle condition once. A second replication was completed approximately 2 months after the conclusion of the first replication, using the same animals, drug doses, and conditions.

Finally, diazepam was tested approximately 6 weeks after the conclusion of the triazolam drug testing. Diazepam was suspended in a mixture of 60% polyethylene glycol and 40% distilled water and injected at 0.0, 1.25, 2.5, and 5.0 mg/kg 30 min before the start of the maze task. As in the earlier drug studies, drug dose administration was completed in a counterbalanced fashion, resulting in each animal's receiving each drug dose and vehicle condition once. A second replication was completed approximately 1 week after the conclusion of the first replication using the same animals, drug doses, and conditions.

**Behavioral measures.** All the behavioral measures were categorized by data reduction Fortran programs that accessed the SKED-11 data. Working memory errors were divided into three categories: initial arm entry (INTA) errors, arm entry (Arm) errors, and nose poke (Poke) errors. INTA errors were assigned when an entry beam break occurred in a baited arm, followed by an entry beam break in a different arm (i.e., when the animal entered and then exited an arm where a pellet delivery had already occurred), followed by an entry beam break in a different arm without an intervening nose poke in the first arm. In other words, an Arm error was counted any time the animal entered, then exited, without making a nose poke in a baited or previously baited arm. Poke errors were classified as any nose poke following a beam break in a previously baited arm. This criterion prevented counting repeated nose pokes as errors during a single arm entry without movement sufficient to break the entry photocell. All the errors were cumulated across the number of correct choices remaining.

As measures of physical mobility and motivation, total number of pellets retrieved, total time (in seconds) in the maze, and total number of arm entries were recorded for each session. In addition, mean arm latency (in seconds) from beam break to nose poke was averaged across all arm choices during each trial and was recorded for each testing session.

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**Figure 1. Zolpidem: Cumulative arm entry and nose poke errors (±SE).**
Data analyses. All the data analyses were completed using SAS statistical software (SAS Institute Inc., Cary, NC). Each drug condition was analyzed independently. The error variables were initially analyzed by using a three-factor repeated measures multivariate analysis of variance (MANOVA), with replication, drug, and correct number of choices remaining as factors. This set of analyses did not result in consistent differences in the error variables between the replications. Therefore, the error variables were averaged across the two replications and then analyzed, using a two-factor repeated measures MANOVA, with drug and correct number of choices remaining as factors. We chose not to present the data for which replication was used as a factor, because there was no consistent difference in the error variables across the replications and because time was not the major issue in this study. Therefore, the averaged data from the two replications were used as a means to stabilize variability in the data. All the remaining variables—total pellets retrieved, total time in maze, total number of entries, and time from beam break to nose poke—were initially analyzed by using a two-factor repeated measures MANOVA, with replication and drug as the factors. Again, because there were no consistent effects from replication, we chose to average across replications and to analyze the data by using a one-factor repeated measures MANOVA, with drug as the factor. Post hoc analyses to identify the source of significant main effects were completed by using Tukey's Studentized range statistic. An alpha level of .05 was used for all post hoc analyses.

RESULTS

Zolpidem

As is shown in Figure 1, zolpidem administration did not result in a drug-related increase in the number of errors committed while completing the eight-arm radial maze. The results from a two-factor MANOVA indicated that none of the error variables (e.g., Arm, Poke, INTA) increased significantly as a function of the drug condition. However, both Arm errors \( F(7,279) = 5.10, p < .0001 \) and Poke errors \( F(7,279) = 5.82, p < .0001 \) increased significantly as the number of correct choices remaining decreased. A post hoc analysis revealed that significantly more Arm and Poke errors were committed while making the last correct choice than in all other correct-choice conditions. None of the error types resulted in a significant interaction between drug condition and correct choices remaining.

The average total number of pellets retrieved, the average total time in the maze, the average total number of arm entries, and the average latency from beam break to nose poke are shown as a function of drug dose in Figure 2. The one-factor repeated measures MANOVA indicated that zolpidem administration did not significantly affect any of these measures.

Triazolam

In contrast to zolpidem, triazolam administration resulted in an increase in the number of Arm errors, Poke errors, and INTA errors (Figure 3). In addition, the number of errors generally increased as the number of correct choices remaining decreased. The results from a two-factor MANOVA indicated that Arm errors \( F(3,279) = 30.73, p < .0001 \), Poke errors \( F(3,279) = 11.52, p < .0001 \), and INTA errors \( F(3,279) = 26.21, p < .0001 \) in-
significantly increased the total time in the maze and the time in the maze
tries. However, triazolam significantly increased the total number of arm entries and the time from beam break to nose poke as a function of drug condition or of the number of correct choices remaining. The results from a two-factor MANOVA indicated that Arm errors \([F(3,279) = 38.63, p < .0001]\) and Poke errors \([F(3,279) = 30.13, p < .0001]\) increased significantly as a function of drug condition. Post hoc analyses revealed that 5.0-mg/kg diazepam resulted in significantly more Arm and Poke errors than did the other diazepam doses and the vehicle. Arm errors \([F(7,279) = 9.40, p < .0001]\) and Poke errors \([F(7,279) = 5.32, p < .0001]\) also increased significantly as the number of correct choices decreased. Post hoc analyses indicated that more Arm errors were made before the last correct choice than before all other correct choices and that more Poke errors were made before the last correct choice than before the first five correct choices. A significant interaction between drug condition and correct choices remaining was found for Arm errors \([F(21,279) = 5.74, p < .0001]\) and Poke errors \([F(21,279) = 4.34, p < .0001]\), indicating that the effect of diazepam on Arm and Poke errors depended on the number of correct choices remaining.

The average total number of pellets retrieved, the average total time in the maze, the average total number of arm entries, and the average latency from beam break to nose poke as a function of diazepam drug dose are shown in Figure 6. The one-factor repeated measures MANOVA indicated that diazepam administration did not significantly affect the total number of pellets retrieved or the total time in the maze. However, diazepam significantly increased the total number of arm entries \([F(3,27) = 12.10, p < .0001]\) and the latency from beam break to nose poke \([F(3,27) = 5.75, p < .01]\). Post hoc analyses revealed that 5.0-mg/kg diazepam significantly increased total number of arm entries and the time from beam break to nose poke, in comparison with the other drug and vehicle conditions.

**DISCUSSION**

The results of the present investigation indicate that both triazolam and diazepam injections resulted in a dose-related increase in the number of errors committed while completing the radial arm maze. In contrast, zolpidem did not result in a similar increase in errors. More specifically, the animals made more arm entry errors than nose poke errors, and the number of errors tended to increase as the number of correct choices decreased following triazolam and diazepam administration. Zolpidem also did not have a negative impact on any of the measures of motor activity used in the present study (pellets retrieved, number of
arm entries, total time to maze completion, latency from arm entry to nose poke). In contrast, triazolam significantly increased the time to maze completion and the latency from arm entry to nose poke, whereas diazepam significantly increased the number of arm entries and the latency from arm entry to nose poke.

These results agree with the general hypothesis put forth by Sanger et al. (1994), that the BZ-1-selective hypnotics may have a different behavioral impact than the non-selective benzodiazepines. An alternative possibility is that the lack of an effect from zolpidem administration could have been the result of too low a drug dose. However, it must be noted that we chose the zolpidem dosage on the basis of the literature indicating that 1.0–3.0 mg/kg of zolpidem resulted in behavioral effects similar to those seen in the benzodiazepines. For example, Griebel et al. (1996) reported that 1 mg/kg of zolpidem and 2 mg/kg of diazepam resulted in similar decreases in motor behavior in an elevated plus-maze task in rats. Another study found that 2.8 mg/kg of zolpidem resulted in less motor activity in the rat in a motor activity cage apparatus than did 2.5 mg/kg of diazepam (Massotti et al., 1991). Similarly, previous studies have shown that the zolpidem and triazolam doses used in the present study have similar motor effects. For instance, zolpidem administration at 1.0 mg/kg was found to have detrimental effects on locomotor activity in mice that were similar to those of 0.08-mg/kg triazolam (Depoortere, 1986). Finally, 2.0 mg/kg of zolpidem and 0.1 mg/kg of triazolam administration in mice have been shown to result in approximately equal numbers of crossings between two compartments in a test box (Sanger et al., 1986).

Another issue when comparing across the three drugs is whether the animals used the same behavioral paradigm to complete the maze task across the experiment. In other words, did the animals use working memory while completing the task for all the drugs, or did they shift their performance to a pattern-type response as they became more accustomed to the maze? It must be noted, however, that the animals were well trained before they were administered zolpidem and had been completing the maze 5 days a week for over 12 weeks prior to the beginning of the experiment. It is also important to note that we specifically discouraged patterning behavior by enclosing the rats in the center of the maze for 5 sec immediately after they exited each arm. During that time, the rats simply ran around the center of the maze, without any clear behavioral pattern emerging. Then, when the doors opened again, the rats would usually dash into the arm that they were nearest but would at times, especially if they were near an arm that they had already entered, walk around and poke their heads into the arms before entering another arm. No clear patterning of behavior was observed for any of the rats. Therefore, it is more likely that the animals were using working memory to successfully complete the task and that both triazolam and diazepam significantly impaired working memory, whereas zolpidem did not.

Therefore, it seems likely that the lack of a significant behavioral effect from zolpidem in the present study was the result of the robust nature of the well-learned radial
Furthermore, it appears that the behavioral and sedative effects of the nonselective benzodiazepines, triazolam and diazepam, overcame any overlearning effect intrinsic to the radial maze task. This would suggest that the behavioral and sedative effects of zolpidem at the present doses were not strong enough to overcome overlearning. Future studies could examine what dosage level of zolpidem is required to overcome performance in a well-learned task, such as the radial maze. However, the present results from a well-learned task support the literature that indicates that zolpidem administration results in less of a negative behavioral impact than does administration of the classic benzodiazepines (Griebel et al., 1996; Sanger et al., 1986; Zivkovic et al., 1992).

When comparing the nonselective benzodiazepines, triazolam and diazepam, at the doses used in the present study, diazepam resulted in more Arm and Poke errors and in more errors being committed as correct choices decreased than did triazolam. These data suggest that, at doses that have been shown to result in a sedative effect, diazepam negatively affected working memory more than triazolam. In contrast, triazolam appeared to have a stronger sedative effect, as is indicated by the greater increase in latency from arm entry to nose poke and by the total time in the maze, in comparison with diazepam. These data are similar to data resulting from a water maze task in which both diazepam and triazolam administration resulted in an increase in the number of errors committed but only triazolam resulted in an increase in the amount of time needed to complete the task (Kant et al., 1996).

As a means of better understanding the relative impact of zolpidem, triazolam, and diazepam on memory and performance in a radial maze task, we can compare the present results to the effects of scopolamine in a task that was identical to that used in the present experiment (Pilcher et al., 1997). In the earlier study, the same methodology as that described here was used, but scopolamine hydrobromide, a well-known anticholinergic that disrupts acquisition of new tasks and performance on previously learned tasks (e.g., Aigner & Mishkin, 1986; Hagan & Morris, 1988) was administered. As was expected, scopolamine administration resulted in an increase in the number of errors committed as a function of drug dose and as the number of correct choices remaining decreased (Pilcher et al., 1997).

Of interest, when comparing the present results with the previous scopolamine results, is that, at doses that did not affect motor behavior, scopolamine induced more than twice the number of Arm, Poke, and INTA errors than did the drugs used in the present study, indicating that scopolamine had a greater detrimental effect on spatial memory in the rat. In fact, it should be noted that, although both triazolam and diazepam resulted in a significant increase in the number of errors committed, the actual number of errors made was quite small. Therefore, although both triazolam and diazepam resulted in a significant increase in errors, they did not have as negative an impact on working memory as scopolamine. Similarly, scopolamine produced a greater number of errors committed as the correct choices remaining decreased than did either triazolam or diazepam, again supporting the conclusion that the effect of triazolam and diazepam on working memory is not as robust as that from scopolamine administration.

In addition to clear detriments in working memory, scopolamine resulted in a significant decrease in the number of pellets retrieved but no change in the number of arm entries. These data suggest that the animals were capable of traversing the maze, since the number of arm entries did not change, but that memory was impaired, since the animals did not retrieve all the available pellets. In contrast, none of the drugs used in the present study resulted in a decrease in the number of pellets retrieved or arm entries, indicating that the sedative effects of the hypnotics did not prevent the animals from successfully completing the task. However, both triazolam and diazepam resulted in an increase in latency from arm entry to nose poke, whereas scopolamine did not. Since animals were capable of mak-
ing the number of arm entries required to complete the maze following benzodiazepine administration, it is not likely that the increase in latency from arm entry to nose poke was indicative of a specific motor impairment. In addition, experimenter observation indicated that the animals were moving around the maze in a normal fashion. Therefore, the decrease in latency from arm entry to nose poke most likely reflected a slowing down of motor functioning owing to the sedative effects of triazolam and diazepam.

Because the process of training the rats in the radial maze and making them drug experienced takes a substantial amount of time, we chose, in the present study, to use the same rats to test all the drug conditions. This does create a circumstance in which carryover effects could take place. However, it must be noted that we completed two independent replications of each drug dose that varied from 1 week apart for diazepam to 2 months apart for triazolam and that we found no significant differences between the replications for any of the drug conditions. Furthermore, it is important to note that all three drugs are considered to be short-acting sleep hypnotics with very short half-lives and little, if any, long-term effect (Balkin et al., 1992; Lister, 1985; Roehrs et al., 1994). Therefore, given that we separated the individual drug testing by at least 1 month, it seems unlikely that the drugs could have had a significant carryover effect.

The results from the present study support the conclusion drawn in other studies (Hodges & Green, 1986; Willner & Birbeck, 1986) that triazolam and diazepam impair working memory in the eight-arm radial maze. However, it must be noted that neither triazolam nor diazepam had as pronounced a detrimental effect on performance as scopolamine administration did in an identical task (Pilcher et al., 1997). In contrast, zolpidem, at the doses administered here, did not have a significant effect on performance. The present data also support the conclusion of other studies (Kant, 1993; Kant et al., 1996; McNamara & Skelton, 1991) that the performance decrement resulting from triazolam and diazepam administration was due to cognitive deficits rather than to motor deficits, in that the apparent sedation did not affect the ability of the animals to complete a well-learned task. Therefore, the present results indicate that the nonspecific benzodiazepines, triazolam and diazepam, had a more pronounced sedative effect, as well as a greater detrimental effect on working memory, in a well-learned radial maze task than did zolpidem, a BZ-1-selective hypnotic. As such, the present data support the theory that the behavioral effects of the benzodiazepines and other hypnotics are related to receptor subtype specificity.

REFERENCES

Aigner, T. G., & Mishkin, M. (1986). The effects of physostigmine and scopolamine on recognition memory in monkeys. Behavioral & Neural Biology, 45, 81-87.
Balkin, T. J., O’Donnell, V. M., Wesensten, N., McCann, U., & Be-

Figure 6. Diazepam: Averaged total number of pellets retrieved, total time in maze in seconds, total number of arm entries, and latency in arm from arm entry to nose poke in seconds (±SE).
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McMillan, D. E. (1982). Effects of chemicals on delayed matching behavior in pigeons. II. Tolerance to the effects of diazepam. Neurotoxicology, 3, 138-141.

McNamara, R. K., & Skelton, R. W. (1991). Diazepam impairs acquisition but not performance in the Morris water maze. Pharmacology, Biochemistry & Behavior, 38, 651-658.

Möller, H., & Okada, T. (1977). Benzodiazepine receptor: Demonstration in the central nervous system. Science, 198, 849-851.

Nicholson, A. N., & Wright, C. M. (1974). Inhibitory and disinhibitory effects of nitazepam, diazepam and flurazepam hydrochloride on delayed matching behavior in monkeys (Macaca mulatta). Neuropharmacology, 13, 919-926.

Piccir, J. J., Sessions, G. R., & McBride, S. A. (1997). Scopolamine impairs spatial working memory in the radial maze: An analysis by error type and arm choice. Pharmacology, Biochemistry & Behavior, 58, 449-459.

Poling, A., Picker, M., Van de Polder, D., & Clark, R. (1986). Chronic effects of ethosuximide, phenytoin, clonazepam, and valproic acid on delayed-matching-to-sample performance of pigeons. Psychopharmacology, 88, 301-304.

Preston, G. C., Broks, P., Traub, M., Ward, C., Poppleton, P., & Stahl, S. M. (1988). Effects of lorazepam on memory, attention and sedation in man. Psychopharmacology, 95, 208-215.

Roehrs, T., Merlotti, L., Zorick, F., & Roth, T. (1994). Sedative memory, and performance effects of hypnotics. Psychopharmacology, 116, 130-134.

Romney, D. M., & Angus W. R. (1984). A brief review of the effects of diazepam on memory. Psychopharmacology Bulletin, 20, 313-316.

Sanger, D. J., Benavides, J., Perrault, G., Morel, E., Cohen, C., Joly, D., & Zivkovic, B. (1994). Recent developments in the behavioral pharmacology of benzodiazepine (omega) receptors: Evidence for the functional significance of receptor subtypes. Neuroscience & Biobehavioral Reviews, 18, 355-368.

Sanger, D. J., Joly, D., & Zivkovic, B. (1986). Effects of zolpidem, a new imidazopyridine hypnotic, on the acquisition of conditioned fear in mice. Psychopharmacology, 90, 207-210.

Schieggert, W., & Schuster, A. (1984). Affinity of various ligands for benzodiazepine receptors in rat cerebellum and hippocampus. Biochemical Pharmacology, 33, 4033-4038.

Smith, C. M. (1984). Drugs and human memory. In D. J. Sanger & D. J. Blackman (Eds.), Aspects of psychopharmacology (pp. 140-173). London: Methuen.

Snapper, A. G., & Ingles, G. B. (1985). SKED-11 software system. Kansas City, MO: State Systems.

Squires, R. F., Benson, D. I., Braestrup, C., Coupet, J., Klepner, C. A., Myers, V., & Beer, B. (1979). Some properties of brain specific benzodiazepine receptors: New evidence for multiple receptors. Pharmacology, Biochemistry & Behavior, 10, 825-830.

Weingartner, H. J., Homer, D., Lister, R. G., Thompson, K., & Wolkowitz, O. (1992). Selective effects of triazolam on memory. Psychopharmacology, 106, 341-345.

Willner, P., & Birbeck, K. (1986). Effects of midazolam and sodium valproate in two tests of spatial behavior. Pharmacology, Biochemistry & Behavior, 25, 747-751.

Zivkovic, B., Perrault, G., & Sanger, D. (1992). Receptor subtype-selective drugs: A new generation of anxiolytics and hypnotics. In J. Mendlewitz & G. Racagni (Eds.), Target receptors for anxiolytics and hypnotics: From molecular pharmacology to therapeutics (pp. 55-73). Basel: Karger.

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