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BRIEF COMMUNICATION

Triazolam in Alzheimer's Disease: Pilot Study on Sleep and Memory Effects

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McCARTEN, J. R., C. KOVERA, M. K. MADDOX AND J. P. CLEARY. *Triazolam in Alzheimer's disease: Pilot study on sleep and memory effects.* PHARMACOL BIOCHEM BEHAV 52(2) 447–452, 1995.—We examined the effects on sleep and memory of a nighttime dose of triazolam, 0.125 mg, in seven subjects with Alzheimer's disease (AD) who were reported by caregivers to be frequently up at night. Subjects were admitted to an intermediate care hospital ward for the 8-day ABA design protocol (placebo baseline–drug–placebo washout). Drug or placebo was given each evening at 2100 h. Sleep was assessed with a wrist-worn activity monitor. Memory was evaluated using a computerized delayed-matching-to-sample (DMTS) task administered at 0800 and 2130 h. Triazolam had no significant effects on total sleep time at night, latency to sleep onset, number of arousals, or time asleep during the day. DMTS performance was significantly worse at night compared to morning during baseline, but there were no significant drug effects. Our results suggest the standard geriatric dose of triazolam, 0.125 mg, may not be an effective hypnotic in AD patients with disrupted sleep, but neither does it substantially worsen the recent memory deficits of AD.

Alzheimer's disease Dementia Memory Sleep Insomnia Triazolam Hypnotic Benzodiazepine Actigraph Delayed-matching-to-sample

ALZHEIMER'S disease (AD), a progressive degenerative brain disease that is the leading cause of dementia in the elderly (14), is often associated with disturbances of the rest/activity pattern (8,43,49,56). Patients with AD frequently develop a tendency to be up at night, creating a major burden for caregivers who must be alert to supervise potentially dangerous behaviors. "Insomnia" is the major proximate reason for nursing home placement of elderly men (42), many of whom undoubtedly have AD.

Complaints of poor sleep are frequent in older adults (7,44), and hypnotics are often prescribed to elderly patients (32,51). A frequently prescribed hypnotic is triazolam (Halcion™), a benzodiazepine with a short serum half life (approximately 3 h) and, therefore, presumably little or no carryover sedation (hangover) the next day (46). Triazolam is an effective hypnotic in healthy persons, but memory impairment and other cognitive changes have been reported following its use, typically at doses of 0.25 mg, 0.5 mg, or higher (6,19). A geriatric dose of 0.125 mg (26) is recommended because age-related changes in pharmacokinetics and pharmacodynmics generally make elderly patients more sensitive to psychoactive medications (29,32,50). The 0.125 mg dose has been shown to increase total sleep time and subjectively improve sleep quality in elderly patients with insomnia or disrupted sleep [for a review, see (25)]. Because of their brain impairment, elderly patients with AD are usually considered to be even more sensitive to many psychoactive medications than healthy elderly. Triazolam, 0.125 mg or even 0.0625 (1/2 tablet of the lowest dose) at bedtime, may be prescribed to patients with AD.

Despite its widespread use, neither the hypnotic efficacy nor the potential adverse side effects of triazolam have been adequately investigated in patients with AD. The potential benefit of successfully treating a behavior problem that often leads directly to nursing home placement is obvious. The potential risk of a medication that may impair mental function in patients who already are a safety risk because of their im-

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paired memory and cognition is also obvious. Both the potential benefits and risks of triazolam use in AD, therefore, are substantial.

We studied the effects of the recommended geriatric dose of 0.125 mg of triazolam on subjects with probable AD who were reported by their caregivers to be up frequently at night. Hypnotic efficacy and acute and carryover effects on memory were assessed.

METHOD

Subjects

The subjects were seven men (mean age = 73, range 62 to 81) with a diagnosis of probable Alzheimer's disease (3,29) followed through the Geriatric Research, Education, and Clinical Center (GRECC) Memory Loss Clinic at the Minneapolis Veterans Affairs Medical Center (VAMC). All lived at home with a spouse or other family member who functioned as the caregiver. Caregivers all complained that subjects were up frequently at night, because of difficulty going to sleep and/or staying asleep, and that such nocturnal sleep disturbances significantly added to the stress and burden of caregiving. (Subjects themselves did not complain of sleep problems or minimized sleep problems.) None of the subjects had a history suggestive of a primary sleep disorder such as sleep apnea, periodic limb movement disorder, REM behavior disturbance, narcolepsy, or insomnia related to drugs, alcohol, medical illness, or psychiatric illness apart from dementia (4). All were in basically good general health with either benign medical histories or well-controlled chronic medical problems. Exclusion criteria were: a history of serious underlying medical illness; alcohol or drug abuse, or major toxin exposure within 10 years of the onset of dementia; a DSM-IV diagnosis other than primary degenerative dementia or a neurological diagnosis other than AD; a Geriatric Depression Scale score (57) of ≥ 14; use of a benzodiazepine for reasons other than sleep; or use of a drug with prominent cholinergic or anticholinergic effects.

Activity Monitoring

Rest/activity patterns were monitored with a portable wrist activity monitor, or actigraph (Ambulatory Monitoring, Inc., Ardsley, NY) a self-contained motion-activated recorder weighing 2 ounces and worn like a wrist watch. The actigraph uses a sensitive accelerometer to detect the presence of movements at a sampling frequency of 10 Hz. A bin size of 30 s allowed the recording and storage of movement data for consecutive 30 s intervals over 8 days. Actigraphs have been used successfully in assessing sleep-wake cycles in AD and other dementias (2,49,56) and in elderly insomniacs (41), and have been used to evaluate the effects of triazolam (38,53). Estimates of sleep onset and duration, number of arousals, and mean activity levels were generated using the available automated scoring system (48), which has demonstrated agreement with formal polysomnographic studies on the order of 90% under a variety of conditions. Nighttime was defined as occurring from 2100 to 0700 h, and daytime from 0700 to 2100 h. (We were not directly concerned with the subjects' complaints of insomnia, which, as noted, were minimal.)

Memory Assessment

Drug effects on recent memory were measured on a computerized titrated delayed-matching-to-sample (DMTS) task using a 13 inch color monitor and touch screen. Subjects matched a sample stimulus (a drawing of a familiar object) with one of four similar choice stimuli, only one of which matched the sample exactly. Each sample stimulus appeared in the middle of the computer screen for at least 6 s. Touching the sample initiated a delay interval of variable length (screen dark), followed by a screen showing the four choices. Recorded messages prompted the subject to touch the sample and the matching choice stimulus, and acknowledged correct choices. Each trial was separated by a 3-s intertrial interval. The position of the correct choice stimulus was randomly varied from trial to trial. The delay interval between sample and choice stimuli was titrated by increasing the delay following a correct response and decreasing the delay following two consecutive incorrect responses. The time added to or subtracted from the delay value with each titration step was fixed for a given subject at 1, 2, 5, 10, or 20 s, determined by the subject's performance in a prestudy assessment. Three consecutive changes from a shorter to a longer delay and back again established the titration value and ended the session. Sessions generally lasted 20 to 30 min, with a maximum of 45 trials. If a titration value was not established by the automated criteria after 45 trials, the highest delay interval at which responding was better than chance was assigned the titration value for that session (see Fig. 1). For subjects functioning at very low levels, a simultaneous match-to-sample (SMTS) trial, wherein the sample stimuli remained in the center of the computer screen when the choice stimuli appeared in the four corners of the screen, and a trial with zero s delay between sample and choice stimuli were employed.

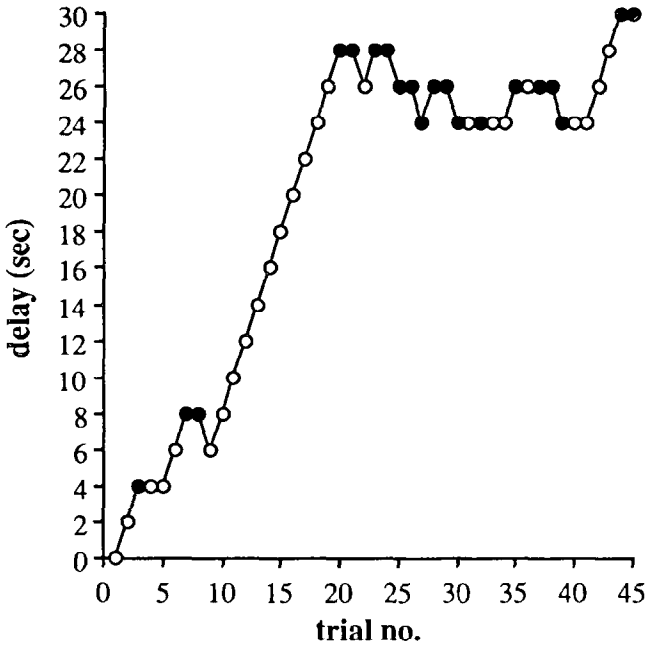

FIG. 1. Titrated delayed matching-to-sample (DMTS). The graph illustrates data from a single session for subject one during baseline. Incremental increases in the delay between sample and choice stimuli were 2 s. Filled circles denote incorrect responses. The titration value is 13, representing the highest incremental increase at which responding was better than chance (25%).

Procedure

Subjects were admitted to private rooms on the GRECC service intermediate care ward, given a general physical and neurological examination, including the Mini Mental State Examination [MMSE; (16)], and allowed 2 days to acclimate to the new setting. A within-subject A-B-A experimental design was employed in which subjects served as their own controls. Subjects were given placebo for 3 nights (placebo baseline), then 0.125 mg triazolam for 3 nights, and then a return to placebo for the final 2 nights (placebo washout). The medication was administered at 2100 h each evening by nurses blind to the drug condition. Beginning at 1800 h, nurses observed and recorded sleep activity at 30-min intervals until 0730 the following morning. The nurse entered the subject's room and observed only long enough to determine and record whether the subject was in bed and if the subject's eyes were open or closed. If the subject was not in bed during normal sleeping hours, the nurse informed the subject where the bed was and that it was bedtime. No other prompts or instructions were given.

Actigraph recordings of patient activity began at 2100 h on the first night of placebo baseline and continued without interruption (except for bathing) until 0700 h the morning following the final placebo washout (hospital day 10, study day 8). Subjects wore the actigraph on the dominant wrist. Actigraph data was analyzed in terms of nighttime (2100 to 0700 h) and daytime (0700 to 2100 h) activity for the 8 consecutive nights and 7 consecutive days of the study.

To assess carryover drug effects on memory, subjects were tested on the DMTS computer test each of the 7 study days at 0800 h. To assess acute drug effects, subjects were tested at 2130 (30 min after drug administration) once during placebo baseline, on night 1 and night 3 of exposure to drug, and once again during placebo washout. Nighttime testing was scheduled to try to capture peak plasma concentration and corresponding maximal cognitive impairment [0.8 to 1.0 h postdose (19)], with sessions beginning before subjects may have fallen asleep if not engaged.

RESULTS

Subject Characteristics

In general, subjects were moderately demented (mean Mini Mental State Examination (MMSE) score = 11.6 ± 6.4 SD, range 4–22) . All were ambulatory, continent, and independent in self-cares (washing, dressing, eating) with minor assistance. The neurological examinations, apart from dementia, were normal. Two of the seven subjects received a scheduled dose of neuroleptic (perphenazine, 2 mg bid in one, and haloperidol 2 mg bid, in the other) before and during the study because of delusions, and a third subject received haloperidol 1 mg as needed for delusions. Another subject was on desipramine, 125 mg per day, because of possible depression, and also received ergoloid mesylates 1 mg per day. Subjects had been on the same doses of medications for at least 8 weeks prior to entering the study. The remaining three subjects were free of psychoactive medications.

Triazolam Effects on Sleep

Group data failed to reveal any significant effect of triazolam on total sleep time at night, latency to sleep onset, number of nocturnal awakenings, total sleep time during the day, or mean level of activity during night or day in the six subjects with complete actigraph data. There was marked interindividual variability in baseline sleep characteristics and in drug effect. Three of the six subjects did show a modest hypnotic response, with average increases in total sleep time at night from 41 to 82 min following triazolam (Fig. 2, subjects 1, 2, and 3). These three responders did not show a consistent decrease in latency to sleep onset following drug, and they actually had more nocturnal arousals (18 ± 4 during baseline, 25 ± 2 during drug, 20 ± 2 during washout). Three subjects, including one responder, one nonresponder, and subject 7, who had only partial actigraph data, had a substantial decrease in total sleep time at night during washout, suggesting a possible withdrawal effect. Nursing observational data was generally consistent with the actigraph data, and indicated that subject 7 probably also had a hypnotic response to triazolam.

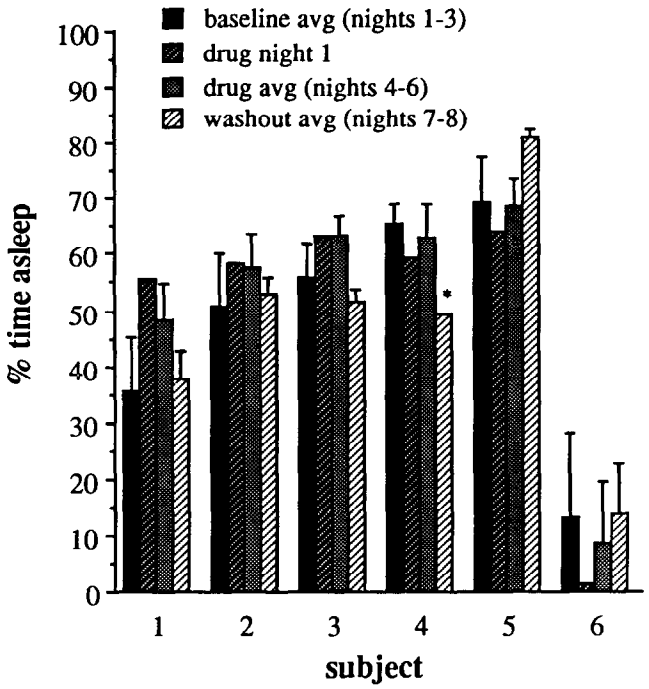

FIG. 2. Actigraph results. Scores are average % ± SD of time asleep at night from 2100 to 0700 h. Placebo or drug (triazolam, 0.125 mg) was administered each night at 2100 h. Note: 1 h = 10% of period examined. *Subject 4 had data for only the first night of washout. [Actigraph data from subject 7 was not complete (no baseline) and is not presented.]

Triazolam Effect on Recent Memory

Three of the subjects performed at very low levels, generating some titration values of 0 s or below (i.e., SMTS). Therefore, data was analyzed in terms of the number of increments the delay value was increased or decreased from 0 delay during each testing session. Performance titrated to 0 s delay counted as 0. A decrease from 0 delay to SMTS was counted as −1. Failure to perform the SMTS was counted −2.

Under baseline conditions, subjects performed better in the morning than at night on the DMTS task (avg incremental increase = 4.8 vs. 3.1, respectively; $p < 0.05$, Wilcoxon

signed ranks test). There were no significant drug vs. placebo effects. As a group, subjects performed significantly worse on nighttime testing drug night 1 vs. drug night 3 (average = 2.6 vs. 4.6, $p < 0.05$). The four subjects who performed worse on drug night 1 compared to the baseline night all slept more following drug. The three subjects whose performance improved or remained unchanged at night following drug did not show an increase in sleep. Decrements in performance relative to baseline generally were mild under any circumstances. One subject showed marked improvement, his best score by far, following acute drug administration on night 3 (16 incremental increases above 0, compared to daytime baseline average = 6.3), despite a typical pattern of performing worse at night on placebo (five incremental increases on both baseline and washout nights).

Correlations Between Triazolam Effect and Sleep Characteristics, Memory, and Other Medications

There was no relationship between response to triazolam and amount of baseline sleep at night (Fig. 2) or during the day. Daytime sleep varied markedly, with the baseline average in three subjects who responded to the hypnotic effect of triazolam = 118 min (range 17–304 min), and in three subjects who did not respond = 79 min (range 16–146 min). Performance on DMTS testing or on the MMSE, or the use of other psychoactive medications also did not reveal any apparent relationship with subjects' response to triazolam.

DISCUSSION

Persons with AD who do not sleep well at night create a common clinical problem that physicians may try to address by prescribing hypnotics. To our knowledge, this preliminary study constitutes the first attempt to evaluate the effects of a commonly prescribed hypnotic medication specifically in patients with AD. In our limited sample of typical male AD patients, our data indicate that the standard geriatric dose of triazolam (0.125 mg) produces no overall group effect. The same dose of triazolam has only mild, if any, deleterious effects on memory in AD, either acutely or on the morning following an evening dose. Though our seven subjects all had typical AD, they were diverse in terms of sleep patterns and performance on the DMTS memory test, and had a broad range of scores on the MMSE. Unfortunately, none of these parameters successfully distinguished those who may have responded to the hypnotic effects of triazolam from those who did not. Indeed, only one of the seven subjects (subject 1) clearly responded to triazolam in a manner consistent with previous reports in the literature: acute worsening of memory functioning following drug, increased time asleep at night, and improved memory functioning in the morning, possibly reflecting improved sleep.

Triazolam, 0.125 mg, has been shown to increase total sleep time over placebo in the elderly, but, consistent with our own findings, most studies have not shown an effect of this dose on sleep latency or number of awakenings (25). Furthermore, its effectiveness has been assessed only in elderly who complain of insomnia and/or have demonstrated sleep disorders, such as central sleep apnea or periodic leg movements (9,10). Our AD patients were reported to be up frequently at night, but did not complain of insomnia and had no evidence, by history, of a primary sleep disorder. The disrupted sleep of typical AD patients may not be comparable to conditions which cause insomnia and/or chronic sleep deprivation, conditions that may increase patients' sensitivity to hypnotics. Many AD patients, instead, may be more comparable to normal volunteers without sleep complaints who also may fail to show an hypnotic response to triazolam (5,28,38). Although their rest/activity patterns are disrupted, AD patients may not be accumulating a sleep debt necessary for standard doses of hypnotics to be effective [see (30), discussion]. This interpretation is consistent with the observation that sedating drugs have no apparent effect on the rest/activity pattern of institutionalized AD patients (56).

The DMTS task was selected to assess memory because it is sensitive to drug effects in animals (40), is easily learned and generates a broad range of performance, has minimal practice effect, is automated, minimizing examiner bias, and tests an aspect of memory that is deficient in AD (11). DMTS performance did show a significant time of day effect consistent with the often observed "sundowning" of demented patients (33). The lack of triazolam effect on the DMTS, either acutely or the next morning, may reflect its lack of hypnotic effect at the dose used.

One subject (subject 5) who did not respond to the hypnotic effect of triazolam, showed a substantial improvement on the DMTS task at night following acute drug administration. Though he did not appear anxious, we speculate that anxiety may have contributed significantly to his memory problems and possibly his sleep disruption. Triazolam may have acted as an antianxiety agent despite its inefficacy as an hypnotic.

Triazolam has been the subject of much controversy in recent years. Detractors claim that the drug has more frequent and serious adverse memory and cognitive side-effects than other benzodiazepines (1,6,23,24,37,52). Others find no substantial evidence for these claims (13,20–22,47). Of the benzodiazepines, those with short half lives and no active metabolites, such as triazolam, are clearly the more appropriate hypnotics in the elderly where residual sedation (12,31,35) and increased plasma concentrations due to reduced clearance (19) may contribute to a variety of problems (30). Drug dose, however, is also an important factor in determining carryover sedation and cognitive impairment (45). Studies that compare triazolam directly with other short- or intermediate-acting benzodiazepines in elderly insomniacs find the various drugs comparable in terms of hypnotic efficacy and cognitive side-effects (22,36).

Alternative hypnotic medications have potentially serious drawbacks and/or no distinct advantages over triazolam. Older agents such as the barbiturates have well-recognized risks of abuse and overdose. Anticholinergic agents, such as diphenhydramine, are often implicated in drug-induced delirium (17,27) and are relatively contraindicated in AD, where the brain cholinergic deficit is well established (39) and correlated with dementia severity (34,55). The newer nonbenzodiazepine imidazopyridine hypnotics, zopiclone and zolpidem, have not demonstrated any clear benefits over triazolam, either in terms of hypnotic efficacy or memory and cognitive side effects (15,18,54). Other agents, such as trazadone, have not been adequately assessed.

Prior to prescribing any hypnotic, it should be remembered that disrupted sleep may result from many different problems. A thorough review of the general medical and sleep history should be conducted with a caregiver familiar with the patient's sleep habits. Special attention should be directed to psychiatric symptoms, such as psychosis, anxiety, and depression, which are common in AD. Primary sleep disorders, such

as sleep apnea, periodic limb movement disorder, and REM behavior disturbance, also may be more common in AD. Medical conditions common in elderly patients, such as chronic pain, orthopnea, and reflux esophagitis, also must be considered in elderly demented patients. Appropriate treatment of a condition associated with sleep disruption may eliminate the need to consider hypnotics.

SUMMARY AND CONCLUSIONS

We did not find a significant effect on sleep or on memory of a bedtime dose of triazolam, 0.125 mg, in a sample of typical male AD patients with disrupted sleep followed in our dementia clinic. A higher dose of the drug may be warranted in AD patients who do not respond to the standard geriatric dose of 0.125 mg, but the effects of an hypnotic dose and repeated administration on consecutive nights have not been assessed in AD.

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