Original Investigations

Effects of Triazolam (0.5 mg) on Sleep, Performance, Memory, and Arousal Threshold

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Abstract. The effects of a short-acting benzodiazepine hypnotic, triazolam (0.5 mg), on sleep, performance, and arousal threshold were assessed in 20 male poor sleepers (age 21 ± 2.37 years). Following a laboratory screening night, all subjects received placebo for 3 nights (single-blind), ten received triazolam and ten placebo for 6 nights (double-blind), and all received placebo on 2 withdrawal nights (single-blind). All effects described below were statistically significant. Triazolam reduced sleep latency and increased total sleep time and sleep efficiency. Percent Stage 2 was increased and percent Stage 4 was reduced during treatment. Morning performance, measured 8.25 h post-drug, showed no decrements. Acute effects were assessed on treatment night 6 during arousals from sleep at 1.5, 3, and 5 h post-administration: performance was impaired in triazolam subjects on the Wilkinson 4-Choice Reaction Time Test, Digit Symbol Substitution Test, Williams Word Memory Test, and Card Sorting Task. In the morning following treatment night 6, long-term memory was tested using a recognition task requiring subjects to identify words presented during nighttime test batteries: triazolam subjects correctly identified fewer target words. Triazolam administration produced anterograde amnesic effects. However, in a Paired Associates Test learned prior to drug ingestion on the previous evening, triazolam did not impair morning recall of word pairs. Threshold for arousal from slow wave sleep was elevated during treatment, and triazolam subjects did not show increased sensitivity to the arousing tone over nights as did placebo subjects.

Key words: Benzodiazepines — Triazolam — Humans — Sleep — Performance — Anterograde amnesia — Arousal threshold

In sleep laboratory studies, triazolam (Halcion), a triazolo-benzodiazepine, has been demonstrated to be an effective hypnotic in doses ranging from 0.25—1.0 mg (Roth et al. 1974, 1977a, 1977b; Vogel et al. 1975, 1976; Kales et al. 1976; Nicholson and Stone 1980; Ogura et al. 1980; Pegram et al. 1980). In addition, results of outpatient studies and other investigations which used self-report measures to evaluate hypnotic efficacy have shown that sleep is subjectively improved after triazolam administration (Veldkamp et al. 1974; Fabre et al. 1977; Fabre and Smith 1977; Leibowitz and Sunshine 1978; Nair and Schwartz 1978; Deberdt 1979; Sundaresan et al. 1979; Hindmarch and Clyde 1980; Piccione et al. 1980).

Pharmacokinetic measures indicate that both triazolam and its active metabolite, 7-α-hydroxy triazolam, have short half-lives, reported to be within the range of 2.1—10 h (Hare 1975; Eberts et al. 1979; Greenblatt et al. in press). The relatively rapid metabolism and clearance of triazolam suggest that, at least at lower doses within the effective range, this benzodiazepine may promote improved sleep without producing a drug-induced performance impairment the following morning. Several studies have assessed morning performance following bedtime triazolam administration (Veldkamp et al. 1974; Vogel et al. 1976; Roth et al. 1977a, 1980; Hindmarch and Clyde 1980; Nicholson and Stone 1980). The results of these studies differ, depending upon dose size, time post-ingestion when test were administered, and the type of tasks used. Only one of these performance studies used insomniacs as subjects (Vogel et al. 1976).

Acute effects of triazolam (0.25 mg and 0.5 mg) on performance have been demonstrated at 3.5 h post-administration in testing following arousal from sleep (Roth et al. 1977a). Nicholson and Stone (1980) have reported an impairment of visuo-motor performance up to 5 h post-administration of a 0.25 mg dose during daytime testing in subjects who remained awake. We believe that ours is the first study of benzodiazepine hypnotics to employ multiple systematic arousals from sleep, designed to delineate temporal parameters of acute effects and provide behavioral correlates of benzodiazepine pharmacodynamics in the sleeping subject.

Materials and Methods

Subjects. Twenty male poor sleepers, mean age 21 ± 2.37 years, were studied. Poor sleep was defined by both subjective and EEG criteria. Subjective criteria included responses to a questionnaire designed to elicit the individual's report of his sleep quality. To qualify for participation, subjects had to identify themselves as "poor" or "very poor" sleepers, report a usual sleep latency of 45 min or longer, and indicate that their sleep problem was "trouble falling asleep" (i.e., sleep onset insomnia) and that this problem had persisted for at least 6 months. The subject's subjective evaluation of his sleep was also discussed in a personal interview. To meet EEG criteria on the screening night, poor sleepers had to exhibit sleep latencies (time from lights out to the onset of Stage 2 sleep) of 30 min or longer and have at least 5% of their total sleep time in slow wave sleep (SWS) (Stages 3 + 4). During

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screening nights, average sleep latency for the 20 subjects was 53.6 ± 34 min.

Subjects were screened for possible psychiatric conditions, sensitivity to benzodiazepines, alcohol or drug abuse, and recent illnesses. All subjects were in good health and denied current or recent use of any type of sleep medication or other drugs. Subjects had no sleep complaints other than those associated with difficulty in falling asleep.

All subjects were informed about the general nature of the experiment and willingly signed Informed Consent and Privacy Act statements. All subjects were asked to refrain from napping and taking drugs or alcohol during the course of the study. Apericri breath analyzer and urine tests indicated no detectable use of alcohol or other drugs during the study.

Based on screening night findings, 20 possible poor sleepers were rejected because of sleep latencies less than 30 min. Two subjects were dropped from the study during placebo-baseline due to concern over poor academic performance. No subjects were dropped because of side effects.

Procedure. A parallel, three-phase design was employed. Subjects who qualified as poor sleepers on the screening night went on to complete 11 additional nights of the 12-night protocol (see Table 1).

Following the screening night, subjects received placebos in a single-blind paradigm for 3 consecutive baseline nights. Following the placebo-baseline nights, ten subjects received 0.5 mg triazolam for 6 nights while the other ten continued to receive placebo in a double-blind paradigm. After the 6 treatment nights, all subjects received placebo on 2 withdrawal nights. The placebo or drug tablet was given at 21.45 hours each night. Lights out was at 22.00 hours and subjects were awakened at 05.30 hours.

Each subject slept in an electrically shielded, air-conditioned room with soundproofing. All electrophysiological variables were recorded on an 8-channel Beckman dynograph. The electrocorticogram (EOG) was recorded from biopotential electrodes placed on the outer canthus of each eye. The EEGs were obtained by use of silver chlorided disc electrodes from C3 and O1 electrode placements referenced to linked mastoids (A1 + A2). Both EOG and EEG time constants were 0.3 s. Sleep stages were determined according to standard criteria (Rechtschaffen and Kales 1968).

Subjects were familiarized with all questionnaires and trained on all tasks in a practice session conducted prior to night 1 of the study.

Bedtime and Morning Questionnaires. The subjects completed a Bedtime Questionnaire each evening which required the subject to report side effects, unusual events occurring that day, naps, alcohol consumption, and his readiness for bed. The Standford Sleepiness Scale (SSS) (Hoddes et al. 1973) was also included in this questionnaire. Upon awakening at 05.30 hours, the subjects completed a Morning Questionnaire which included the SSS and also required the subject to estimate sleep latency, total sleep time, and number of awakenings, to list any physical complaints, and to rate the effectiveness of the pill and evaluate sleep quality.

Sleep Measures. Sleep latency (time from lights out to the onset of Stage 2) was scored for all study nights. Mean sleep latencies were derived for each subject for each condition: placebo-baseline (nights 2 – 4), treatment (nights 5 – 10), and placebo-withdrawal (nights 11 – 12).

Sleep stage data were obtained for statistical comparisons on nights 2, 5, 7, 11, and 12. On these nights, other study procedures for obtaining arousal threshold, auditory evoked responses (AEPs), and night-time performance measures, were not conducted. Sleep measures were: total sleep in minutes (the sum of minutes in Stages 2, 3, 4, and REM); Stage 1 percent (minutes of Stage 1 divided by total bedtime × 100); Stage 2 percent, Stage 3 percent, Stage 4 percent, and Stage REM percent (minutes in each stage divided by total sleep × 100); sleep efficiency (total sleep divided by total bedtime × 100); wake time (minutes awake while in bed); wake percent (minutes awake divided by total bedtime × 100). For analyses by conditions, sleep measures were derived as follows: placebo-baseline (night 2), treatment (mean of nights 5 and 7), and placebo-withdrawal (mean of nights 11 and 12).

Morning Performance and Mood Testing. Performance and mood test batteries were administered approximately 20–40 min after the morning awakening following nights 1, 2, 4, 5, 7, 9, 10, 11, and 12. Data from testing following the screening night (night 1) were not included in the data analysis. Morning batteries included two subjective mood scales, the NHRC Mood Scale and the Profile of Mood States (POMS), and several performance tests, including the Wilkinson 4-Choice Reaction Time Test (performed for 11 min) and the Digit Symbol Substitution Test. These tests have been described in detail in a previous publication (Church and Johnson 1979). The test battery also included the Williams Word Memory Test (Williams and Williams 1966): this task is a test of short-term memory. Subjects heard a tape-recorded list of 15 words. The voice on the tape said each word, spelled the word, and then repeated each word again. During list presentation, the subject wrote down each word. At the end of the 15-word presentation, the subject was