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SUMMARY

The changes seen in EEG activity with administration of long-acting benzodiazepines are a significant decrease in delta, 0.5−3 Hz, and a significant increase in sleep spindles, bursts of 11−15 Hz activity. These changes often persist for several days after the medication is discontinued.

The introduction of a new benzodiazepine hypnotic, triazolam, in which the half-life of both the parent compound and its metabolite is less than 10 hours, raises questions as to whether its use will produce similar EEG changes during sleep and whether there will be a build-up effect over nights. Of particular interest is whether electrophysiological and performance changes will persist at the same level during a 7.5-hour sleep period and whether there will be a quick return to baseline EEG activity during withdrawal. As part of a larger study on the effects of benzodiazepines on EEG, sleep, arousal levels, and performance, delta and spindle activity were measured during baseline, treatment, and withdrawal. The auditory cortical evoked potential was also obtained during the last baseline and during the fifth drug night.

Twenty male chronic poor sleepers, mean age 21.02 ± 2.37 years, with EEG measured sleep latencies of greater than 30 minutes, participated in the double-blind study. All received a placebo for 3 nights, 10 continued to receive the placebo and 10 were given 0.5 mg triazolam for 6 nights, and all received placebo on 2 withdrawal nights. Subjects received click stimulation on the last night of the baseline and the fifth night of hypnotic administration (study nights 4 and 9).

Subjects receiving triazolam showed a significant increase in sleep spindles and a significant decrease in delta count during drug administration. Both values returned to baseline on the first withdrawal night. The auditory evoked potential (AEP) peak-to-trough amplitude was also significantly reduced during sleep by triazolam, but, as the time since drug ingestion increased, the amplitude of the AEP also increased. There was no difference in AEP amplitude between the two groups 5 hours post-drug ingestion.

In morning performance batteries, there were no cognitive or visual motor performance decrements. While the long-acting metabolites of some benzodiazepines, further influenced by dose levels, may be the neuropharmacological basis for daytime performance decrements, these data indicate that the EEG changes occur in the absence of long-acting metabolites. As with flurazepam, there was no relationship between the EEG changes, sleep efficiency, and morning performance.

INTRODUCTION

The changes in EEG defined nonREM (NREM) sleep with benzodiazepine use are usually a decrease in slow wave sleep (SWS), particularly in stage 4 sleep, and an increase in stage 2. Computer analyses of the delta activity during sleep of patients taking flurazepam have consistently demonstrated a decrease in delta amplitude,[1,2] and Johnson et al.[3] reported a decrease in number of delta waves, as well as a decrease in delta amplitude. The number of sleep spindles in NREM sleep is increased in most patients with the administration of benzodiazepines,[4-7] and, for some patients, the sleep spindle rate/minute doubles after 3 or 4 nights of use.[1,3]

The introduction of a new benzodiazepine, one in which the half-life of both the parent compound and its metabolite is reported to be less than 10 hours, raises questions as to whether similar EEG changes will occur during sleep and whether there will be a build-up effect over nights. Of particular interest is whether electrophysiological and performance changes will persist at the same level during a 7.5-hour sleep period and whether there will be a quick return to baseline EEG activity during withdrawal. In a study by Johnson et al.,[1] it was found that the increased spindle rate/minute remained well above baseline 3 nights after the discontinuation of flurazepam, whose metabolite, N-desalkyl-flurazepam, has a half-life of 24 – 48 hours.[8] Kales et al.[9] as well as Vogel et al.[10] have found that when sleep was monitored during withdrawal from long-acting benzodiazepines such as flurazepam, there was no rebound insomnia, but rebound insomnia was reported in patients taking short-acting benzodiazepines.

Triazolam is a short-acting benzodiazepine that has been found to be an effective hypnotic.[11-13] In an earlier report, the half-life of the parent drug was reported to be 5 – 10 hours, and that of its active metabolite, 7-α-hydroxy-triazolam, 3 – 10 hours.[14] Greenblatt et al.[15] have recently reported that for 0.5 mg triazolam, the peak concentration occurred 0.25 hours after ingestion and the elimination half-life was 3.1 hours. As part of a larger study on the effects of benzodiazepines on EEG, sleep, arousal levels and performance, delta and spindle activity were measured during baseline, treatment, and withdrawal. The auditory cortical evoked potential was also obtained during the last baseline and during the fifth drug night. There have been conflicting reports of the effect of triazolam on SWS[10,11,16-20] but, in general, the reported triazolam-related decreases in SWS have been of smaller magnitude than those reported with the longer-acting benzodiazepines. There are no computer-based reports detailing the triazolam-related changes in delta and spindle counts or their effects on the evoked potential.

METHODS

Subjects

Twenty male poor sleepers, students in the Naval School of Health Sciences, mean age 21.02 ± 2.37 years, were studied. Poor sleep was defined by both EEG and subjective criteria. Subjective criteria included responses to a questionnaire designed to evaluate an individual's estimate of his sleep quality, followed by personal interview. To qualify as a poor sleeper, subjects had to rate their sleep quality as "poor" or "very poor" and indicate a usual sleep latency greater than 45 minutes. To meet EEG sleep criteria, poor sleepers had to exhibit sleep latencies of 30 minutes or more on a screening night. During screening nights, average sleep latency was 53.6 ± 34 minutes. All subjects had more than 5% of their total sleep time (TST) in stages 3 + 4.

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. There were no sleep complaints other than those associated with 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. Breath analyzer and urine tests, used aperiodically, indicated no detectable use of alcohol or other drugs during the study.

During screening night, 20 possible poor sleepers were rejected because of sleep latencies less than 30 minutes. Two subjects were dropped from the study during placebo baselines due to concern over poor academic performance. No subjects were dropped because of side effects.

Procedure

Following the screening night, subjects received placebos in a single-blind paradigm for 3 consecutive baseline nights. Following the baseline nights, 10 subjects received 0.5 mg triazolam for 6 additional nights while the other 10 continued to receive placebo in a double-blind paradigm. Following the 6 treatment nights, all subjects received placebo on 2 withdrawal nights. The placebo or drug tablet was given at 2145 hours each night. Subjects were put to bed at 2200 and awakened at 0530.

Each subject slept in an electrically shielded, air-conditioned room with soundproofing. All electrophysiological variables were recorded on an 8-channel Beckman dynograph. The electro-oculogram (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 C_3 and O_1 electrode placements referenced to linked mastoids ($A_1 + A_2$). Both EOG and EEG time constants were 0.3 seconds. Sleep stages were determined according to standard criteria.[21]

On-line EEG analysis. Detection of delta half-waves (0.5–2 Hz) and sleep spindle bursts (11.75–15 Hz) was accomplished on-line using the Smith phasic EEG detector.[22] The detector output was counted by the detector's digital counters and also printed out in 2-minute epochs by a printer. At the end of the sleep period, the total number of delta half-waves and the number of sleep spindles were available both from the counters and the printed output. The comparability of measures of spindle and delta activity, as obtained via use of the Smith on-line analysis and off-line computer analysis, was previously demonstrated during a study of flurazepam.[3] EEG analyses were performed on the nights of uninterrupted sleep; e.g., the subject was not awakened to determine arousal thresholds or to perform tasks. EEG analysis was done for placebo baseline nights 2 and 4, treatment nights 5, 7, and 9, and on withdrawal nights 11 and 12. Clicks below arousal threshold were delivered on nights 4 and 9, but comparison of night 4 with night 2, and night 9 with night 7, revealed no significant differences in the spindle or delta activity.

Auditory evoked responses. Subjects received click stimulation on the last night of the baseline and the fifth night of drug administration (nights 4 and 9). Clicks were delivered over a loudspeaker attached to the head of the bed, approximately 46 cm over the subject's head as he

laid in bed. The procedure was as follows: for 10 minutes prior to lights out, clicks (10 msec duration, 73 dB SPL) were presented once every 16 seconds while the subject laid quietly in bed and focused his eyes on a target on the ceiling. Clicks were discontinued at lights out (2200 hours). Following sleep onset, click presentation (48 dB SPL) was again begun and continued throughout sleep, except when the EEG indicated transitory waking or stage 1. To reduce possible awakening, for the first 5 subjects, the click dB level was reduced when an arousal was seen. It soon became apparent that this could create a problem in analysis of the evoked response, and the dB level was held constant on both nights for the remaining 15 subjects. Click intensity was kept relatively low (48 dB SPL) so as not to disturb sleep. If an arousal occurred, the click was turned off until the sleep was stable again. Because our subjects had recently passed naval entrance hearing examinations, hearing was tested only in terms of subjective threshold for a 2-second, 1000 Hz tone presented on other nights of the study. Presleep thresholds varied between 36–38 dB SPL. Details of the instrumentation for presentation of the click and the off-line PDP-12 computer analysis of the evoked responses are presented in an earlier paper.[3]

RESULTS

As has been previously reported, triazolam significantly reduced sleep latency and increased sleep efficiency. While the sleep latency during withdrawal returned to placebo baseline levels, there was no "rebound" insomnia. There also was no significant difference between the placebo and triazolam subjects on cognitive and visual motor tests given in the morning. The detailed analysis of sleep and performance data will be presented elsewhere.

Though none of the sleep parameters were significantly different between the placebo and drug groups, on the placebo baseline sleep night (which was night 2 of the study), the drug group had a longer sleep latency, 51 ± 36 minutes vs. 35 ± 16 minutes for the placebo group. As the total bed time was fixed at 7.5 hours, the longer sleep latency for the drug group resulted in their having less TST. The drug group also had less NREM time, 259 vs. 272 minutes, but the REM times were almost identical, 115 vs. 118 minutes, respectively, for the drug and placebo groups. Because of the group differences in TST and NREM on the placebo night, difference scores (treatment minus placebo, treatment minus withdrawal, and withdrawal minus placebo) were used in all the statistical analyses. All statistical tests for delta, spindle, and averaged evoked potential analyses were evaluated at the 0.05 level and were one-tailed. Significant results were checked by use of comparable nonparametric statistics.

Spindle Count

The spindle and delta analyses were done in NREM sleep only. As has been found with other benzodiazepines, during the treatment period (nights 5–10), the subjects receiving triazolam showed a significant increase in spindle rate/minute. These data are presented in Table 1. The t-test, based on placebo minus treatment difference scores between groups, was highly significant for the treatment period ($t_{18} = 4.04$, $p < 0.0005$). In contrast to flurazepam, however, there was a quick return of the spindle rate to baseline on the withdrawal nights. The between-groups t-test, performed on the placebo-baseline minus withdrawal scores, was not significant ($t_{19} = 0.85$). These results are presented in Fig. 1 for the uninterrupted sleep nights during which spindle count was obtained. The increase in spindle rate for triazolam subjects was significant from baseline on the first drug night (night 5) ($t_9 = 2.89$, $p < 0.01$), and the increase from night 5 to

night 7 was also significant ($t_9 = 1.83$, $p < 0.05$). The increase in spindle rate reached a plateau by the third drug night (night 7) and no further increase was seen on the fifth drug night (night 9). The graph clearly reflects the return to baseline for the triazolam subjects on the first withdrawal night (night 11).

TABLE 1

SPINDLE ACTIVITY PER MINUTE DURING NREM SLEEP

Group	Condition		
	Placebo (Night 2)	Treatment (Nights 5 and 7)	Withdrawal (Nights 11 and 12)
	$\bar{X}$ ± (S.D.)	$\bar{X}$ ± (S.D.)	$\bar{X}$ ± (S.D.)
Placebo	3.36 (1.31)	3.24 (1.57)	3.55 (1.41)
Triazolam	3.97 (2.23)	5.69 (2.69)	3.86 (1.95)

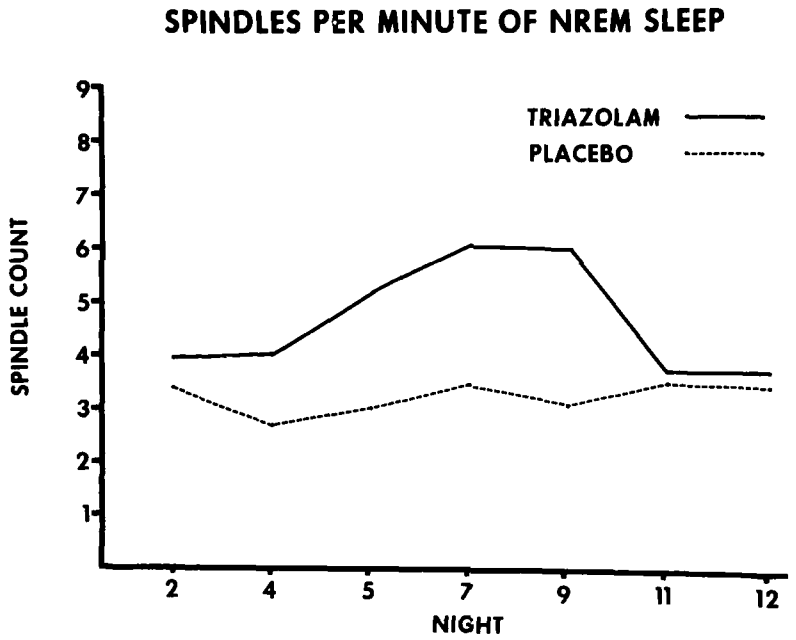

Fig. 1. Spindle count/minute during placebo baseline nights 2 and 4, treatment nights 5, 7, and 9, and withdrawal nights 11 and 12.

Delta Count

The effect of triazolam on delta count also followed the expected pattern (Table 2). There was a significant decrease in number of delta half-waves/minute. The delta count/minute results for placebo, baseline, treatment, and withdrawal during NREM sleep are presented in Table 2. The t value for comparison of between-group difference scores (placebo-treatment) was $t_{18} = 3.88$,

$p < 0.005$. As with spindle count, there was a return to baseline during the withdrawal nights. The t value for between-group difference scores (placebo-withdrawal) was $t_{18} = 1.34$, n.s. These results, over nights, are presented in Fig. 2. The decrease in delta count for the triazolam group was significant from placebo baseline on the first night of drug intake (night 5) ($t_9 = 5.39$, $p < 0.005$), and the decrease on night 7 was also significant when compared to night 5 ($t_9 = 1.86$, $p < 0.05$). The maximum decrease in delta count was on the third drug night (night 7). As noted earlier, the maximum increase in spindle rate was also seen on the third drug night. Fig. 2 also illustrates the return to baseline for delta count on the first withdrawal night (night 11).

TABLE 2

DELTA HALF-WAVE COUNT PER MINUTE DURING NREM SLEEP

Group	Condition		
	Placebo (Night 2)	Treatment (Nights 5 and 7)	Withdrawal (Nights 11 and 12)
	$\bar{X}$ ± (S.D.)	$\bar{X}$ ± (S.D.)	$\bar{X}$ ± (S.D.)
Placebo	40.92 (20.83)	39.65 (19.89)	39.66 (17.72)
Triazolam	47.52 (25.90)	32.08 (23.89)	37.66 (27.39)

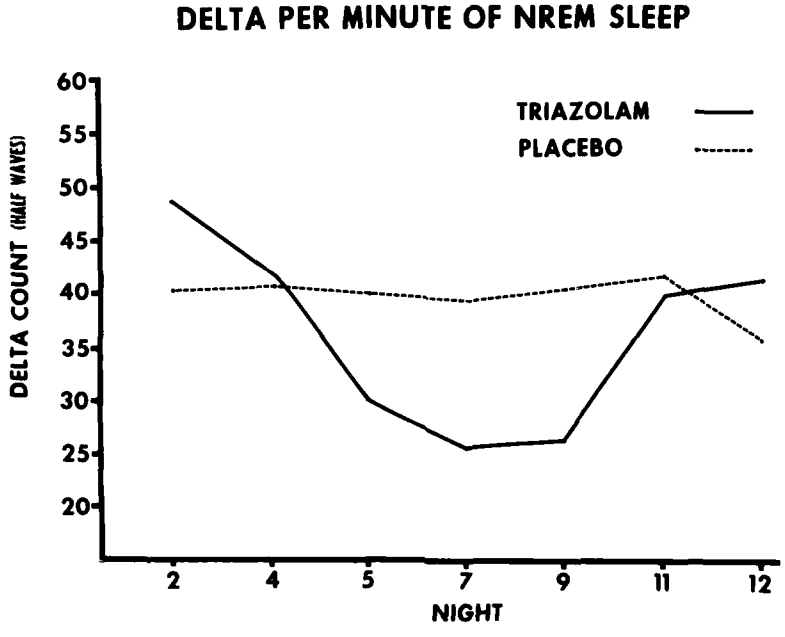

Fig. 2. Number of delta half-waves/minute during placebo baseline nights 2 and 4, treatment nights 5, 7, and 9, and withdrawal nights 11 and 12.

Auditory Evoked Potential (AEP)

As indicated in the methods section, the click dB level for the first 5 subjects was not constant during the night. The data from 4 other subjects were also not analyzed due to technical difficulties. The AEP analysis, therefore, included data from 6 triazolam and 5 placebo subjects.

The analysis was performed for AEPs obtained in awake, stage 2, stages 3 and 4 (SWS), and in REM sleep. The stage 2 and stage REM analyses were also done by thirds of the night. Comparison between groups and within groups was made by use of peak-to-trough amplitudes. Since the AEP wave form is modified during sleep, in lieu of the usual labeling conventions such as N_1, P_2, N_2, P_3, an illustration of the AEP wave form for awake, REM, and NREM, with the measured peak and trough underlined, is presented in Fig. 3. These peak-to-trough indices were chosen because of their consistency from subject to subject and over the night. The mean number of trials summed for each AEP did not differ significantly between the two groups for any of the comparisons. The number of trials for the two groups over the 2 nights varied from 27 to 34 for awake, 494 to 548 for all-night stage 2, 271 to 297 for all-night stage REM, and 175 to 215 for all-night SWS. For stage 2 analysis by thirds of the night, the minimum number of trials was 124 and the maximum was 229. For REM analysis by thirds of the night, the range of trials analyzed varied from 68 to 141. The mean peak-to-trough amplitude, standard deviations, and the t values for between-groups difference scores are presented in Table 3.

The amplitude of AEPs recorded while the subjects were awake prior to lights out did not differ for the two groups during baseline nor when the treatment-minus-baseline difference scores were compared.

TABLE 3

MEAN AEP PEAK-TO-TROUGH AMPLITUDE (μV)

	Placebo Group		Triazolam Group		t and p values (difference scores)	
	Night #4 $\bar{X}$ ± (S.D.)	Night #9 $\bar{X}$ ± (S.D.)	Night #4 $\bar{X}$ ± (S.D.)	Night #9 $\bar{X}$ ± (S.D.)		
Waking	22.00(6.04)	19.80(3.56)	25.17(8.21)	21.20(11.19)	0.1159*	
Stage 2 (1st 3rd)	39.60(15.44)	51.00(16.93)	48.73(18.73)	26.83(11.51)	5.5680	0.0005
Stage 2 (2nd 3rd)	34.40(7.47)	38.60(13.05)	39.33(18.67)	22.50(8.87)	1.9902	0.05
Stage 2 (3rd 3rd)	35.20(12.52)	39.80(8.17)	44.17(20.27)	32.67(14.81)	1.5831	n.s.
Stage 2 All night	37.60(10.45)	43.40(12.64)	42.67(18.50)	23.83(6.43)	3.3146	0.005
REM (1st 3rd)	6.20(3.70)	8.80(3.70)	11.33(5.16)	8.50(3.02)	2.2124	0.05
REM (2nd 3rd)	8.80(2.17)	7.60(2.19)	8.80(3.19)	8.33(2.50)	1.0660*	n.s.
REM (3rd 3rd)	6.20(1.79)	8.00(1.87)	7.67(2.42)	8.00(2.28)	1.1194	n.s.
REM All night	6.80(2.17)	7.40(2.30)	8.17(2.93)	7.50(1.64)	1.0679	n.s.
SWS(3+4) All night	60.60(17.52)	66.00(19.38)	64.50(12.01)	40.83(4.96)	4.1377	0.005

*Indicates df = 8, all others have df = 9.

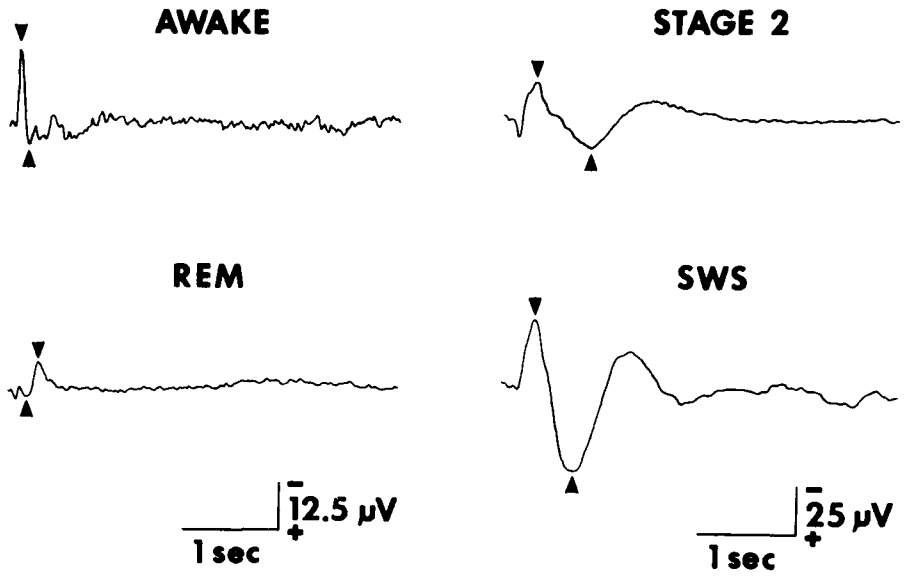

Fig. 3. Arrows indicate wave used for AEP peak-to-trough amplitude measure for awake and stages of sleep.

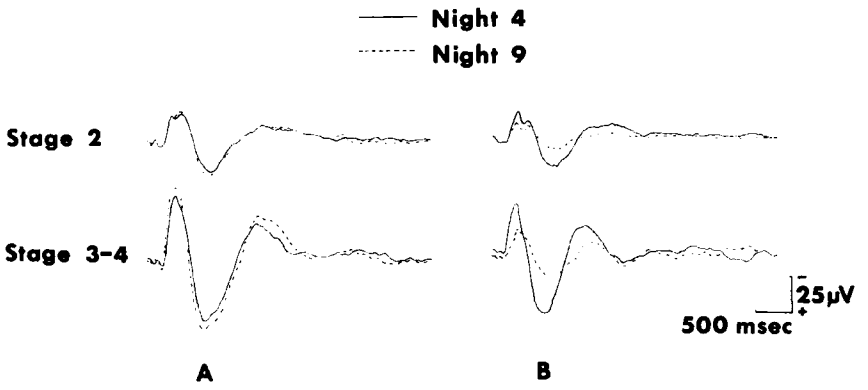

Fig. 4. AEP during stages 2 and 3–4 from nights 4 and 9 for a poor sleeper who received placebo on both nights (section A), and for a poor sleeper who received triazolam on night 9 (section B).

There was a significant decrease in AEP amplitude in the triazolam subjects for stage 2 and SWS for trials averaged over the entire night. This decrease in AEP during stage 2 and SWS is illustrated in Fig. 4 for one subject. The response between the two groups, averaged over the entire night, was not significantly different during stage REM. During the first third of the night, however, there was a significant decrease in peak-to-trough amplitude in the AEP during REM sleep of the triazolam subjects. For stage 2, the potential was significantly reduced during the first and second thirds of the night. These results for stage 2 are illustrated in Fig. 5.

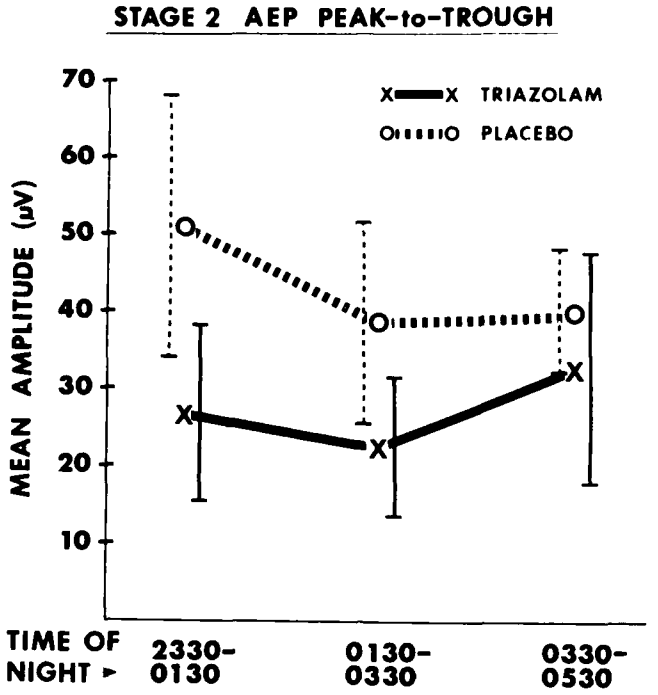

Fig. 5. Change in AEP with time since ingestion of 0.5 mg triazolam. Note that, over the night, the AEP amplitude for triazolam subjects increased while that for placebo subjects decreased.

DISCUSSION

Though it has a half-life of only 5–10 hours for the parent compound, and 3–10 for its metabolite, we found that triazolam produces similar EEG changes during sleep to those produced by long-acting benzodiazepines. But we also found differences between our flurazepam and triazolam data. These differences appear to be related to the long half-life of the active metabolite of flurazepam, since the half-life of flurazepam itself is very short.[8]

While the spindle count was still elevated on the third withdrawal night after 10 nights of 30 mg flurazepam administration,[1] on the first night of withdrawal from triazolam, there was a return to placebo baseline levels for both delta and spindle count. The absence of significant drug activity during withdrawal is also reflected in the return to placebo sleep latency values.

The rapid metabolism of triazolam is further reflected in the increase in the amplitude of the AEP as the time since drug ingestion lengthens. During the first 3 hours post-drug ingestion, there was a significant decrease in the AEP in triazolam subjects during all stages of sleep. The AEP, averaged over the 5–7.5 hours post-ingestion time period, showed no significant decrement in any stage of sleep.

A similar post-drug response curve was found for performance data. On the sixth drug night (study night 10), we awakened the subject 1.5, 3, 5, and 7.5 hours post-drug, and tested him on a battery of cognitive and visual motor performance tasks. The 7.5 hours post-drug was the

scheduled morning awakening. The performance decrement was similar to that seen for the AEP. These data will be reported in detail elsewhere, but for one task (the 4-choice reaction time test), the average reaction time values, in milliseconds, for the triazolam subjects were 1020, 1139, 908, and 598, respectively, for the 1.5, 3, 5, and 7.5 hours post-drug testing sessions. The comparable mean reaction times for the placebo subjects were 650, 676, 717, and 558. Note the similarity of the two groups at 7.5 hours post-drug.

To our knowledge, this study was the first to measure the time course of drug effect during sleep on the EEG and on behavioral response through systematic arousals of the sleeping subject. Most sleep studies have looked at early morning and subsequent daytime performance. The time course of the behavioral effects following drug ingestion has also been studied in subjects who remain awake during the entire study period. It is of interest that, for triazolam at least, the time course of drug effects on performance tasks is the same regardless of whether the subject remains awake, or is allowed to sleep and is awakened to perform. Nicholson and Stone,[19] using a 0.25 mg triazolam dose level and a 0.4 mg brotizolam dose level,[23] reported a similar temporal change on a visual motor (tracking) task. Though the Nicholson et al.[23] findings and ours cannot be directly compared, the similarity of results on visual motor tasks suggests that whether the subject is awake or asleep is not a major factor in the pattern of the performance change post-drug and, perhaps, in the rate of drug metabolism.

The gradual increase in spindle rate and decrease in delta count over the first 3 nights of drug administration are surprising in light of the return to baseline on the first night without drug. The EEG changes over nights suggest that a minimal level of the drug is still in the body 24 hours later. The level, however, is not large enough to produce an EEG change or to function as a hypnotic, but of sufficient amount to potentiate the effect of an additional dose. These EEG changes plateau after the third drug night, suggesting that the drug level reaches a plateau. Blood level studies would, of course, be necessary to verify these inferences made from EEG data.

There is still no consensus as to the role of delta activity or sleep spindles during sleep, or to the significance of their change to awake behavior. As in our previous work,[3,24] we found no relationship in this study between subjective estimates of sleep quality and the amount of change in delta or spindle activity. The similarity on morning tasks and in mood between our placebo and triazolam subjects once again attests to the negligible influence of number or amplitude of delta waves and rate of spindles/minute on awake performance.

Irwin Feinberg (personal communication) has raised the possibility that methodological differences might account for some of the reported differences in the magnitude of change in delta activity among studies. Azumi and Shirakawa[7] have indicated that the Rechtschaffen and Kales[21] recommendation for spindle activity, 12–14 Hz waves with burst duration of at least 0.5 Hz, may be too restrictive. They recorded activity in the 11–16 Hz range and felt this broader frequency range was more representative of spindle frequencies. Though the quantitative data may differ depending on methodological grounds, there has been no disagreement as to the type of EEG changes produced by the benzodiazepines.

In their paper, Azumi and Shirakawa offered two possible neuropharmacological explanations for the increase in spindles. One of their hypotheses was related to the gamma amino butyric

acid (GABA) intensifying effects of the benzodiazepines,[25,26] and to the reports by Andersen and his colleagues[27-29] and Rhodes[30] that spindle waves originate from an increase of inhibitory post-synaptic potentials (IPSPs) in thalamic neurons. With these two considerations, GABA potentiation by benzodiazepines and sleep spindles as an IPSP of thalamic neurons, in mind, Azumi and Shirakawa assumed that the originating mechanism of spontaneous spindles is facilitated due to the intensifying inhibitory action of a GABA-like substance, or some other inhibitory neurotransmitter by benzodiazepines.

As an alternative, these authors, using findings from the clinical area, speculated that the increase in spindles may be due to hypofunction of an inhibitory system, mainly located in the frontal cortex. This inhibitory system has an influence on lateral nuclei of the thalamus.[31,32] "Therefore, if administration of benzodiazepines results in hypofunction of the cortex to some extent, an increase of spindles would follow."[7]

Perhaps, in time, the function and significance of sleep spindles and delta activity will be found, but, even without this knowledge, these EEG measures can be used as sensitive electrophysiological indices of the presence of benzodiazepines and their metabolites, and perhaps of other drugs in the central nervous system.

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(U) The effects of the short-acting benzodiazepine, triazolam, on EEG activity during sleep were assessed in poor sleepers. Twenty male subjects, mean age 21 ± 2.37 years, participated. A screening night preceded 3 placebo nights, 6 treatment nights, and 2 placebo-withdrawal nights. During treatment, 10 subjects received triazolam (0.5 mg) and 10 received placebo. The treatment condition was double-blind. In addition to rate/min spindle count and number of

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20. ABSTRACT (continued)

delta half-waves/min, the auditory evoked response (AEP) was obtained on the last placebo baseline and the fifth drug night.

Subjects receiving triazolam showed a significant increase in sleep spindles and a significant decrease in delta count during drug administration. Both values returned to baseline on the first withdrawal night. The AEP peak-to-trough amplitude was also significantly reduced during sleep by triazolam, but, as the time since drug ingestion increased, the amplitude of the AEP also increased. There was no difference in AEP amplitude between the two groups 5 hr post-drug ingestion.


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