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Temazepam's efficacy in patients with sleep onset insomnia

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1 The hypnotic efficacy of temazepam capsules (30 mg) was studied in twelve patients who had objective polysomnographic evidence of sleep onset insomnia. Patients slept in the laboratory, retiring at their usual bedtime after taking placebo or temazepam 30 min earlier, and were monitored for 8 h using standard polysomnographic techniques.
2 Acute (nights 5–7) and chronic (nights 11–13) temazepam improved the sleep of these patients by reducing sleep latency and increasing sleep time compared to the placebo baseline (nights 2–4).
3 No detrimental effects on daytime function the following morning were observed using questionnaires and objective tests of performance.
4 No consistent evidence of disturbed sleep after discontinuation of treatment was obtained over three recovery nights.

Keywords temazepam sleep insomnia benzodiazepines

Introduction

Temazepam in the hard capsule formulation available in the United States has been shown in double-blind, placebo controlled, clinical trials to relieve complaints of difficulty falling asleep, frequent awakenings, and early morning awakenings (Fillingim, 1979, 1982; Heffron & Roth, 1979). However, three sleep laboratory studies, while demonstrating temazepam's overall hypnotic efficacy, did not confirm the perception of reduced sleep latency found in the clinical trials (Bixler *et al.*, 1978; Mitler *et al.*, 1979; Vogel, 1983, personal communication). This lack of an effect on sleep latency could be the result of experimental methodology in the sleep laboratory studies previously conducted (i.e. objective confirmation of sleep onset insomnia, time of drug administration, Bixler *et al.*, 1978). Thus, in the present study polysomnographic measures of sleep were evaluated in patients with objectively determined difficulty falling asleep (sleep latency greater than 30 min) rather than patients with primary sleep maintenance problems.

Methods

Subject selection

Twelve adults, either males or females not capable of childbearing, between 21 and 60 years of age, were chosen for this study. All were in good health, except for their sleep complaints, as indicated by the results of a physical examination, history, and clinical laboratory tests. Candidates were excluded if there was evidence of significant gastrointestinal, hepatic, renal, or other systemic abnormalities, or a history of drug addiction, alcoholism, known hypersensitivity to benzodiazepines, or if they required concomitant CNS medication during the study.

Patients were selected who complained of insomnia based on a sleep history and 1 week of sleep diaries. The subjective criteria of insomnia were: sleep induction of 30 min or greater, total sleep time of 6 h or less or three or more awakenings per night. The polysomnographic criteria of insomnia obtained on the mean of the three baseline nights were a latency to persistent sleep

of 30 min or longer and between 240 and 420 min of total sleep time during the 480 min recording. Patients were excluded if there was evidence of nocturnal myoclonus, restless legs, sleep apnoea, or other sleep disorder as the cause of their sleep complaint.

Design

Temazepam (30 mg) in the hard capsule formulation available in the United States was administered, double-blind, with placebo baseline and recovery periods preceding and following the active medication. On the first four nights, which were the adaptation and baseline screening nights, all patients received placebo. Patients eligible based on the polysomnographic criteria then received temazepam (30 mg) capsules for nine consecutive nights. For the last three nights all patients again received placebo.

Procedure

Patients reported to the sleep laboratory on nights 1 to 7 and 11 to 16 approximately 1 h before their usual bedtime which was held constant throughout the study. They completed a pre-sleep questionnaire and an adverse reaction form. Electrodes were attached at conventional placements for continuous recording of the EEG (C3 and 0z), EOG, and EMG (submental). Medication was administered 30 min before bedtime and patients then spent 8 h in bed. Each morning within 1 h after arising and dressing patients completed the post sleep questionnaire. The questionnaire asked for estimates of total sleep time, number of awakenings, time to fall asleep, time of final awakening and for evaluations of the depth and quality of sleep. Their performance on the Symbol Copying and Digit Symbol Substitution Tests also was assessed.

On nights 8 to 10, patients slept at home and were instructed to follow the same procedures as on laboratory nights. Appropriate medication for each night was supplied in an envelope, and all envelopes with the time of administration recorded on each were to be returned to the laboratory on night 11.

All patients were instructed not to consume alcohol or any other medication during the course of the study. On all nights coffee, tea, or cola were not allowed after 19.30 h. Also naps were not permitted during the study.

Each polysomnographic recording was scored manually in 30 s epochs according to the standards of Rechtschaffen & Kales (1968).The scorers were unaware of the experimental condition. The mean of the three-nights of baseline, acute drug administration, chronic drug administration, and recovery for each patient was computed for all polysomnographic and subjective sleep parameters and the safety parameters. To evaluate the effect of drug administration, comparisons between baseline and acute, baseline and chronic, and baseline and recovery were made using repeated measures analyses of variance and *post hoc* *t*-tests. Wilcoxon Signed-Ranks Tests were used where assumptions of the *F*-test were violated (post-sleep questionnaire and daytime alertness questionnaire). A comparison between the acute and chronic administration was made to evaluate the development of tolerance. Finally, comparisons between baseline and the first night (night 5) and last night (night 13) of drug administration and the first night of recovery (night 14) were made.

Results

Patient characteristics

The background characteristics of the patients, including the nature of their sleep complaints, are presented in Table 1. There was an equal number of men and women. All patients reported difficulty falling asleep with latencies of approximately 1.5 h. All patients also had difficulty maintaining sleep and felt their total sleep time was inadequate. Two patients complained of early morning awakenings. All rated their sleep problem as being moderate or severe and the majority felt their problem was a chronic one.

Baseline polysomnographic measures of sleep can be found in Table 2 which presents the data as means over the baseline (nights 2–4), acute drug (nights 5–7), chronic drug (nights 11–13), and recovery (nights 14–16) periods. On baseline these patients took a mean of 54 min to fall asleep (latency to stage 2). They slept for a mean total of 6.5 h, awakening on the average seven times for a total of 30 min over the 8 h recording. They did not awaken much earlier than their scheduled arising time 8 h after lights out; wake after sleep (WAS) was only 5 min. Thus these patients primarily had sleep onset insomnia.

Drug effects on polysomnographic measures of sleep

Sleep induction Drug effects on sleep induction were evaluated using the parameters latency to stage 2 sleep, latency to persistent sleep (10 continuous min of nonwake recording), and wake

Table 1 Patient characteristics and sleep complaints

Subject	*Age (years)*	*Sex*	*Estimated latency (min)*	*Nocturnal awakenings Number*	*Duration (min)*	*Estimated TST (h)*	*Early awakening (Y/N)*	*Severity (mi, mo, sev)*	*Type (A, S, C)*	*Hypnotic use (Y/N)*
01	21	M	60	3	60	6.0	N	Mo	S	N
02	30	F	120	12	60	5.0	N	Mo	S	N
03	36	M	45	3	105	5.5	N	Mo	S	Y
04	21	F	90	3	60	5.0	Y	Mo	C	N
05	46	F	60	3	60	6.0	N	Mo	S	N
06	30	M	45	4	195	4.0	N	Sev	S	N
07	27	M	180	4	60	4.0	N	Sev	C	N
08	22	F	120	5	120	5.0	Y	Sev	C	N
09	25	F	60	4	240	3.5	N	Sev	C	Y
10	23	M	120	3	90	4.5	N	Mo	C	N
11	28	M	120	3	60	4.5	N	Sev	C	N
12	45	F	120	4	120	4.0	N	Sev	C	Y
Mean	29.5		95	4.3	102.5	4.75				
s.d.	8.7		41.6	2.5	59.6	0.81				

time before sleep (WBS). Both acute and chronic temazepam administration significantly reduced WBS ($F = 8.27$, $P < 0.001$) and the latencies to stage 2 sleep ($F = 8.08$, $P < 0.001$) and persistent sleep ($F = 8.25$, $P < 0.001$). There was no difference in latencies between acute and chronic drug administration. On recovery all induction parameters returned to baseline levels.

Sleep maintenance The parameters wake during sleep (WDS), wake after sleep (WAS), and number of awakenings were used to assess temazepam's effect on sleep maintenance. Temazepam reduced the number of awakenings ($F = 5.46$, $P < 0.01$) and WDS ($F = 3.37$, $P < 0.05$) with both acute and chronic administration. WAS was not affected by drug administration. However as noted earlier, the majority of patients in this study did not complain of early morning awakenings. Their baseline values were quite low and the variability quite high making it difficult to demonstrate a drug effect. On recovery the number of awakenings and time awake (WDS) returned to baseline.

Overall efficacy Temazepam's overall efficacy was evaluated with the parameters total sleep time (TST) and percent wake (%W). Both acute and chronic administration of tempazepam affected these measures, increasing TST ($F = 13.4$, $P < 0.001$) and reducing %W ($F = 13.4$, $P < 0.001$). On recovery these parameters returned to the baseline levels.

Sleep staging The acute and chronic administration of temazepam increased percent stage 2 sleep ($F = 19.25$, $P < 0.001$) and the latency to REM sleep ($F = 9.42$, $P < 0.001$). There were no differences in acute and chronic administration. Only chronic administration had an effect on percent stage REM sleep, decreasing it ($F = 3.97$, $P < 0.05$). There were no differences in any of these parameters between baseline and recovery periods.

Drug effects on nights 5, 13 and 14

The efficacy of temazepam on the first night (night 5) and the last night (night 13) of administration and the effect of drug discontinuation on the first recovery night (night 14) was evaluated. These comparisons were made using the polysomnographic measures of sleep. The results did not differ appreciably from those found for the mean data. Temazepam was effective on the first and last night of administration. On the first recovery night these parameters returned to baseline levels.

Table 2 Polysomnographic measures of sleep

	Baseline	*Acute*	*Chronic*	*Recovery*
(a) *Efficacy*				
1) Induction				
Latency to Stage 2	53.7 ± 32.45	24.6 ± 10.00	28.7 ± 14.33	43.5 ± 19.57
Latency to Pers S1	54.6 ± 32.11	23.8 ± 10.56	30.0 ± 15.26	43.1 ± 20.31
WBS	53.5 ± 32.47	22.6 ± 9.77	27.0 ± 14.41	41.1 ± 20.49
2) Maintenance				
WDS	29.5 ± 23.10	13.4 ± 9.66	12.7 ± 8.98	20.2 ± 16.01
Number of awakenings	6.7 ± 4.15	3.1 ± 2.22	4.1 ± 3.44	4.6 ± 2.89
WAS	5.5 ± 9.46	2.0 ± 4.56	7.1 ± 11.34	13.8 ± 20.10
3) Overall				
TST	391.5 ± 28.29	441.7 ± 15.45	432.6 ± 22.60	404.9 ± 37.84
% W	18.4 ± 5.88	7.9 ± 3.25	9.7 ± 4.65	15.6 ± 7.89
(b) *Sleep staging*				
% Stage 1	12.1 ± 5.25	8.6 ± 4.34	8.3 ± 3.49	10.9 ± 5.92
% Stage 2	59.1 ± 5.58	66.1 ± 5.03	67.3 ± 5.49	57.1 ± 7.32
% Stage 3–4	7.3 ± 5.35	5.7 ± 5.81	5.2 ± 5.46	8.1 ± 7.07
% Stage REM	21.5 ± 4.63	19.4 ± 4.45	19.2 ± 3.46	23.7 ± 5.56
Latency to REM	88.6 ± 33.73	119.4 ± 38.75	134.0 ± 38.95	76.5 ± 27.1

Baseline = nights 2–4; Acute = nights 5–7; Chronic = nights 11–13; Recovery = nights 14–16.

Drug effects on subjective sleep parameters

Subjective assessments of sleep collected on the post-sleep questionnaire were compared using the Wilcoxon Signed Ranks Test ($P < 0.05$). Comparisons were made between baseline and acute drug, baseline and chronic drug, baseline and recovery, and acute and chronic drug. The patients felt their sleep latency was reduced from baseline after both acute and chronic administration of temazepam. They also experienced a small difference in sleep latency between the acute and chronic periods. On recovery estimated sleep latency was the same as baseline. Temazepam, acute and chronic, reduced the number of awakenings patients reported compared to baseline and during recovery they continued to awaken less frequently. Again there was a difference between the acute and chronic periods. The degree of early awakening was re-

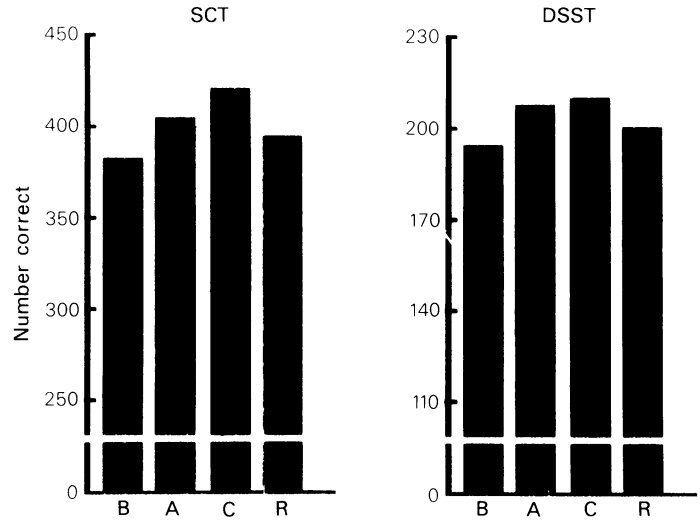

Figure 1 Number of correct Symbol Copying Test (SCT) responses and Digit Symbol Substitution Test (DSST) responses during baseline (B), acute drug (A), chronic drug (C), and recovery (R) periods.

duced and total sleep time was increased with acute and chronic temazepam. There were no differences on these two parameters between acute and chronic or baseline and recovery periods. Compared to baseline, patients felt they slept more deeply with acute and chronic temazepam and their sleep quality was improved after the acute administration. No differences on these parameters between baseline and recovery or acute and chronic periods were found.

Safety parameters

The risks associated with temazepam administration were assessed with a daytime alertness and side effects checklist completed each night before bedtime. Daytime residual effects were evaluated using the Digit Symbol Substitution Test (DSST) and the Symbol Copying Test (SCT). The same four comparisons, described previously, were made among the different periods of the experiment. No differences on any of the comparisons were found on the daytime alertness and side effects questionnaire. There was no evidence for a daytime residual effect on performance. In fact, after acute and chronic administration of temazepam SCT performance was improved compared to baseline levels ($F = 4.85$, $P < 0.01$). DSST performance did not change reliably with temazepam. On recovery SCT scores returned to baseline indicating that the change was not merely a practice effect. Figure 1 illustrates these changes in performance.

Long term effects of temazepam administration were examined by comparing the pre- and post-experiment clinical laboratory data. No clinically significant changes on any of the tests were found.

Discussion

Temazepam capsules effectively reduced the sleep latency of patients with objectively verified sleep onset problems. This reduction in sleep latency was found on both polysomnograhic and subjective measures. Therefore, the failure of previous studies to show a statistically significant effect on polysomnographic measures of sleep latency was probably due to the heterogenity of the patient population studied (patients with primarily sleep maintenance problems) or the time of drug administration (e.g. lights out). In the present study, patients primarily with sleep latency problems were evaluated. In the initial screening patients had to show a mean latency to stage 2 sleep of 30 min or greater; mean baseline latency was 54 min. Interestingly in studies of healthy normals whose sleep latencies were relatively short (less than 30 min) results also have been inconsistent. Using the soft gelatin formulation 20 mg temazepam reduced the sleep latency of young subjects but not middle age subjects even though they had similar mean latencies (about 22 min) under placebo conditions (Nicholson & Stone, 1976, 1978). This pattern of results led Mitler (1981) to conclude in a recent review that temazepam probably reduces sleep latency only in people whose baseline latency exceeds 30 min. Our results support Mitler's conclusion.

In understanding any hypnotic's effect on sleep latency, particularly temazepam, several other factors must be considered in addition to the nature of the study population. One factor is the rate of absorption. The hard gelatin capsule, available in the United States, produces peak plasma concentrations within 3 h and the soft gelatin capsule, available in Great Britain, within 20 min (Mitler, 1981). A peak concentration may not be necessary to produce a therapeutic effect, but clearly the hard capsule is more slowly absorbed. Dose also is important. The doses studied in the United States have been 15 and 30 mg, while in Great Britain lower doses, 10 and 20 mg, have been used. Finally, time of administration relative to initiation of the recording is critical. In this study treatment was administered 30 min before initiating the recording. All these factors, formulation, dose, time of administration relative to recording initiation, and the nature of the study population interact to produce the effect on sleep latency. The question remains whether the differences in dissolution and absorption between the two formulations are clinically meaningful.

Replicating previous sleep laboratory and clinical studies, temazepam was found to effectively maintain sleep and increase its duration. All maintenance parameters were improved by at least 50% and total sleep time was increased by 50 min. Patients also perceived the depth and quality of their sleep as improved.

These beneficial effects of temazepam occurred without significant side effects or daytime residual effects. In fact, performance was improved after the chronic administration of temazepam. Patients with complaints of insomnia usually feel that their sleeping difficulties impair their ability to function during the day. One would then expect that improvements in sleep would also lead to improved daytime function. These data show a statistically significant improvement in one measure of daytime function accompanying an improvement in sleep.

On discontinuation of temazepam there was

no consistent disruption of sleep. Mean total sleep time on the first recovery night or over all three recovery nights was similar to the baseline level. An inspection of the individual data found that two patients had shorter sleep (less than 95%) on one recovery night compared to their baseline and two patients had shorter sleep on two recovery nights. In other words, disturbed sleep occurred in four of the 12 patients on 6 of the 36 recovery nights studied.

To summarize, temazepam capsules (30 mg) improved the sleep of patients with insomnia, by reducing sleep latency and increasing sleep time. These benefits were found from the first treatment night to the final treatment night. No detrimental effects on daytime performance or safety were observed and no consistent evidence of disturbed sleep with discontinuation of treatment was obtained.

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