Br. J. clin. Pharmac. (1979), **8**, 63S-68S

HYPNOTIC EFFICACY OF TEMAZEPAM: A LONG-TERM SLEEP LABORATORY EVALUATION

M.M. MITLER*, MARY A. CARSKADON, R.L. PHILLIPS†, W.R. STERLING‡, V.P. ZARCONE, JR, R. SPIEGEL§, C. GUILLEMINAULT & W.C. DEMENT

Sleep Research Center, Stanford University School of Medicine, Stanford, California 94305

1 Temazepam was evaluated in a strictly defined insomniac patient population under sleep laboratory conditions. Two protocols were used: a short-term (26-night) and a long-term (54-night) protocol evaluated the efficacy of the drug administered at night at 15 mg (short-term study) and 30 mg (long-term study), respectively.

2 Temazepam seemed to be both safe and effective at doses of 15 and 30 mg with up to 5 weeks of ingestion.

3 Suppression of slow wave sleep was observed at the high dose, but no suppression of REM sleep, found in studies with other benzodiazepines, was noted.

4 No evidence was found for development of tolerance or rebound effects.

Introduction

IN recent years, the necessity of evaluating hypnotic compounds on chronic insomnia volunteers in the sleep laboratory has been increasingly emphasized. Insomnia is frequently a chronic complaint and treatment often involves long-term administration of hypnotic compounds; thus, the pattern of therapeutic use requires that evaluation of these compounds include both short-term and prolonged administration. As part of a general effort in sleep research to find safe and effective hypnotic agents, we have undertaken the evaluation of a new benzodiazepine compound, temazepam. The study was carried out using two protocols: a short-term (26-night) protocol assessed the efficacy of temazepam 15 mg at night during 14 consecutive nights of ingestion; and a long-term protocol (54 nights) evaluated the efficacy of temazepam 30 mg at night over 5 weeks of administration. Tolerance and dependency were addressed in the long-term study, which included both an immediate and a prolonged withdrawal condition.

Present addresses: *Department of Psychiatry, State University of New York, Health Sciences Center, Stony Brook, New York 11794; †Department of Cardiology, Stanford University School of Medicine, Stanford, California 94305; ‡Sandoz, Inc., East Hanover, New Jersey 07936; §c/o Sandoz Ltd, Department of Experimental Therapeutics, 4000 Basel, Switzerland.

0306-5251/79/160063-06 $01.00

Methods

Subject selection

Subjects (age range 40-65 yr) were physically normal male volunteers or females who were post-menopausal, hysterectomized or otherwise unable to bear children. General guidelines for subject selection included a history of chronic insomnia of six months or more, characterized by sleep difficulty not associated with significant psychopathology. Additionally, subjects were selected who demonstrated three or more of the following conditions in a prestudy screening recording: (1) objective sleep latency of more than 15 min; (2) objective total sleep time of less than 6.5 h; (3) at least 30 min of objective wake time after sleep onset and before the final morning awakening, unless total sleep time was 5 h or less; or 20 or more awakenings per night as defined by 50% or more of EEG alpha wave in a 30^{-s} epoch; (4) daytime complaints of sleepiness, jitteriness, or fatigue.

Table 1 presents baseline means for total sleep time, sleep latency, wake time after sleep onset, and number of awakenings for subjects in both protocols. Eleven subjects had marked sleep disturbances as evidenced by their baseline records. Subjects were randomly assigned to either protocol, with the restriction that the subjects be able to comply with all requirements of the study. Volunteers agreed to be drug-free and to refrain from drinking alcohol or coffee within 3 h of bedtime.

Before the studies, medications in the form of hard gelatin capsules were sealed in individual envelopes, labelled with the subject's name and the protocol night. Inactive placebo capsules of identical appearance to temazepam were given on the nights indicated in Tables 2 and 3. Medications were taken 15 min before bedtime, with minimal variation during the course of the studies. Each subject was assigned individual sleeping quarters in the laboratory. Bedrooms were identical, each containing a twin-sized bed, desk, chair and lamp. A preset bedtime for each subject was determined according to the subject's habitual bedtime, and each subject was allowed to sleep until awakening spontaneously in the morning. Every effort was made to ensure a minimum of 7 h total dark time every study night. A subject who awakened before the 7 h minimum was encouraged to try to sleep a little longer. No time cues, e.g., watches, clocks or sunlight in the laboratory, were available to the subjects.

Sleep was recorded in the standard manner from EEG (C_3/A_2 or C_4/A_1), differential electro-oculogram and bipolar electromyogram from chin muscles. Sleep recordings were scored by trained technicians using the criteria of Rechtschaffen & Kales (1968). On every morning of the studies, subjects completed a questionnaire on which they commented about the quality of sleep and estimated sleep latency, duration of sleep and number of arousals.

Statistical analyses

Data from sleep recording and morning questionnaires for Tuesday, Wednesday and Thursday (non-adaptation, laboratory nights) of each week were analyzed statistically. The principal statistical tool was the repeated-measure analysis of variance. Analysis was carried out separately for each variable. Conditions and nights were treated as repeated measures, with seven subjects in each analysis. Interpretation of F ratios involved the conservative Greenhouse–Geiser approach (Winer, 1962). Thus, for evaluating significance levels the first member of the degrees of freedom expression was always 1 and the second n—1 (that is, 6). This report summarizes the evaluation of the following parameters: objective sleep latency, objective total sleep time, wake-time after sleep onset, slow wave sleep time, REM sleep time, subjective sleep latency, subjective total sleep time and subjective number of arousals.

Contrast statistics were performed on all possible

Table 1 Age, sex and baseline means of objective sleep variables

Subject	*Sex*	*Age*	*Total sleep time (min)*	*Sleep latency (min)*	*Waketime after onset (min)*	*Number of arousals*
Short-term study						
AA	F	55	379.8	17.7	15.3	13.6
LC*	F	58	259.9	83.8	30.5	6.0
PH	F	51	383.0	23.0	66.0	18.3
JM	M	54	336.7	3.1	44.2	14.7
BN	M	52	251.5	76.7	58.2	31.1
CO	M	50	315.6	1.3	52.3	18.3
HS	M	51	289.9	11.9	53.7	8.9
BW	F	51	387.6	19.7	35.4	12.0
$\bar{X}$		52.8	325.5	29.6	44.4	15.4
s.d.		2.7	55.3	32.2	16.6	7.6
Long-term study						
GA	F	61	298.5	9.3	8.1	6.7
DC	M	54	252.6	16.4	34.3	13.6
NG	F	53	390.2	58.9	56.1	18.7
DG	M	46	412.8	13.5	45.7	32.7
RL	F	52	290.4	34.1	84.6	12.0
LM	F	62	354.7	3.7	9.6	6.4
HQ	F	53	351.8	9.5	32.1	8.4
JS*	F	61	343.4	40.5	83.7	26.9
$\bar{X}$		55.3	336.8	23.2	44.3	15.7
s.d.		5.6	53.4	19.3	29.5	9.7
Criterion value		40-65	390.0	15.0	30.0	20

*These patients completed their respective studies, but were dropped for further statistical analyses because patient LC was found to be taking a concomitant medication in violation of the protocol and patient JS required a reduction in dosage.

pairwise comparisons when the overall F ratio was significant beyond the 0.10 level. These contrasts were in the form of simultaneous t-tests using the epsilon correction for heterogenity of the population covariance matrix (Huynh, 1978) and the improved t-table for multiple contrasts of Games (1977).

Results

Table 4 lists the mean values for the variables analyzed in the short-term study; and Table 5 presents analogous means from the long-term study.

Sleep induction and maintenance

Analysis of variance showed no significant decrease in sleep latency in either study, although there was a clear trend for reduced sleep latency on the first drug condition in both studies.

Sleep maintenance was evaluated from the recorded total sleep time and the wake time after sleep onset. There was a significant main effect of conditions on total sleep time in the short-term ($F = 6.1$; $df = 1,6$; $P < 0.05$) and long-term ($F = 11.2$; $df = 1,6$; $P < 0.01$) studies, wherein sleep-time was prolonged during the drug administration period.

Wake-time after sleep onset, which gives a measure

Table 2 Experimental protocol for short-term (26-night) study

Night	*Placebo*	*Temazepam (15 mg)*	*Lab*	*Home*	*Condition*
1-2	×		×		Adaptation
3-5	×		×		Baseline
6-7	×			×	
8-9	×		×		Readaptation
10-12		×	×		Drug 1
13-14		×		×	
15-16		×	×		Readaptation
17-19		×	×		Drug 2
20-21		×		×	
22-23		×	×		Readaptation
24-26	×		×		Recovery

Table 3 Experimental protocol for long-term (54-night) study

Night	*Placebo*	*Temazepam (30 mg)*	*Lab*	*Home*	*Condition*
1-2	×		×		Adaptation
3-5	×		×		Baseline
6-7	×			×	
8-9	×		×		Readaptation
10-12		×	×		Drug 1
13-14		×		×	
15-16		×	×		Readaptation
17-19		×	×		Drug 2
20-21		×		×	
22-23		×	×		Readaptation
24-26		×	×		Drug 3
27-28		×		×	
29-30		×	×		Readaptation
31-33		×	×		Drug 4
34-35		×		×	
36-37		×	×		Readaptation
38-40		×	×		Drug 5
41-42		×		×	
43-44		×	×		Readaptation
45-47	×		×		Recovery 1
48-49	×			×	
50-51	×		×		Readaptation
52-54	×		×		Recovery 2

of the continuity of sleep throughout the night, was also significantly improved by temazepam. In the short-term study, there was an almost significant main effect of conditions ($F=4.97$; $df=1,6$; $P<0.10$). Similarly, in the long-term study there was an almost significant condition effect ($F=5.35$; $df=1,6$; $P<0.10$).

For total sleep time and wake-time after sleep onset in both studies, contrast statistics disclosed that the main effects were due entirely to the differences between drug conditions versus baseline and withdrawal conditions. There were no significant contrasts within the drug conditions.

Sleep structure

The structure of sleep was assessed using the variables of slow wave sleep time and REM sleep time (Tables 4 and 5). In the short-term study, there were no significant effects on slow wave sleep time, although there was a trend for reduced slow wave sleep during the drug periods. In the long-term study, on the other hand, there was a significant decrease in slow wave sleep time across conditions ($F=8.01$; $df=1,6$; $P<0.05$).

Contrast statistics disclosed that the major effect was due to a reduction in slow wave sleep time

Table 4 Effects of temazepam 15 mg at night in the short-term study

*Variables**	*Baseline*	*Drug 1*	*Drug 2*	*Recovery*
Sleep latency and maintenance				
Objective sleep latency	21.9	13.7	23.0	30.2
Objective total sleep time	337.1	397.1	375.4	326.6
Wake-time after sleep onset	46.8	20.3	21.0	51.2
Sleep structure				
Slow wave sleep (stages 3 and 4)	40.9	33.5	24.3	28.8
REM sleep	60.7	79.6	72.8	70.6
Subjective estimates				
Subjective sleep latency	24.0	17.7	20.8	46.4
Subjective total sleep time	344.3	387.4	381.4	322.1
Subjective number of arousals	2.9	1.0	2.0	4.0

*All values are in minutes except subjective number of arousals.

Table 5 Effects of temazepam 30 mg at night in the long-term study

*Variables**	*Baseline*	*Drug 1*	*Drug 2*	*Drug 3*	*Drug 4*	*Drug 5*	*Recovery 1*	*Recovery 2*
Sleep latency and maintenance								
Objective sleep latency	20.8	14.7	25.3	26.3	25.6	20.8	32.4	18.2
Objective total sleep time	321.0	431.6	378.7	366.3	368.1	395.0	300.8	368.2
Wake-time after sleep onset	40.4	14.9	14.9	22.6	17.3	21.3	56.6	33.0
Sleep structure								
Slow wave sleep (stages 3 and 4)	38.1	15.0	16.2	4.8	9.3	9.1	14.0	25.9
REM sleep	72.4	83.1	71.4	70.2	69.4	73.1	64.9	90.0
Subjective estimates								
Subjective sleep latency	53.8	30.4	35.9	33.8	32.5	29.3	59.0	33.6
Subjective total sleep time	318.8	396.4	360.5	348.8	357.1	389.3	289.9	351.0
Subjective number of arousals	1.8	2.6	2.3	2.9	1.8	0.9	4.5	2.7

*All values are given in minutes except for the subjective number of arousals.

throughout the drug conditions. This reduction in slow wave sleep time as compared with baseline persisted through the first recovery period in the long term study ($P < 0.01$).

REM sleep time showed no significant changes across conditions in either study.

Subjective estimates

Estimates of sleep latency in the short-term study showed an almost significant conditions effect ($F = 5.77$; $df = 1,6$; $P < 0.10$). In the long-term study, subjective estimates of sleep latency were not significantly shortened, although there was a trend for reduced estimates of latency during the active medication periods.

In contrast, the subjective estimates of sleep time in the short-term study were not significantly lengthened by drug administration. Estimated sleep times in the long-term study, however, were probably affected across conditions ($F = 5.40$; $df = 1,6$; $P < 0.10$) in which the sleep time estimates were higher during the drug conditions than in non-drug conditions.

Subjective estimates of the number of arousals disturbing night-time sleep were unaffected by the drug in either study.

Adverse reactions and clinical laboratory findings

Although the dosage was reduced from 30 mg to 15 mg in one subject because of nystagmus, there were no other systematic adverse side-effects, physical or psychological, in either study. In addition, clinical laboratory evaluations (haematological and urinalysis) carried out periodically in both groups revealed no significant abnormalities.

Discussion

Temazepam seems to be effective in prolonging and maintaining sleep at doses of 15 mg and 30 mg. In addition, this efficacy was apparent throughout prolonged administration of the 30 mg dose. Contrast statistics disclosed no indication of tolerance for as long as 5 weeks of drug ingestion at the 30-mg dose level. Furthermore, there was no suggestion of recovery conditions showing poorer sleep than baseline levels, that is, rebound insomnia (Kales *et al.*, 1978).

Sleep latency however, was not significantly improved by the compound, although there was an overall trend for reduction in this parameter. This failure to decrease sleep latency may be related to subjects' generally short sleep latencies before drug ingestion or to the short interval between drug administration and lights out.

The structure of sleep, as evaluated using slow wave and REM sleep times, was not significantly affected by the lower dose in the short-term study. On the other hand, the compound, like other benzodiazepines (Dement *et al.*, 1978; Kales *et al.*, 1975), significantly reduced slow wave sleep at the higher dose level. In addition, this slow wave sleep suppression persisted throughout the drug administration period and seemed to affect recovery sleep as well. This reduction in slow wave sleep may be at least partially explained by the fact that visual scoring was done. Feinberg *et al.* (1977) have shown that direct quantification of delta-wave activity discloses no clear benzodiazepine reduction in delta-wave sleep. REM sleep was unaffected at either dose level.

Subjectively, the insomniac volunteers generally reported greater speed of sleep induction and prolonged sleep during the period of active drug administration. These results were significant for sleep latency in the low-dose, short-term group and for sleep time in the high-dose, long-term group. The number of arousals reported by subjects was unaffected at either dose level.

In summary, temazepam seemed to be both safe and effective at doses of 15 mg and 30 mg with up to 5 weeks of ingestion. The compound seems to be very similar to flurazepam in its hypnotic efficacy and suppression of slow-wave sleep at high doses (Dement *et al.*, 1978) but it did not suppress REM sleep as has been found in several studies of flurazepam (Kales *et al.*, 1971; Kales *et al.*, 1975). Moreover, in the variables analyzed, there was no evidence suggesting the development of drug tolerance due to long-term temazepam administration and no evidence of rebound insomnia due to abrupt withdrawal.

At this point several cautionary comments are appropriate. The study was carried out in 1974 when patient selection for hypnotic efficacy work was based on strict objective criteria. Sleep latency and total sleep time were computed for each candidate beforehand, and patients presenting with conditions reported to be associated with a complaint of insomnia such as nocturnal myoclonus, sleep apnea, and so on, were eliminated. In a recent survey it was found that out of 114 unselected patients who came to the Stanford Sleep Disorders Clinic with a subjective complaint of insomnia during a 3-month period in 1978 only 24 fitted the requirements to enter the reported study. This fact underlines the newly identified drawbacks inherent in evaluating a drug's safety and efficacy in one diagnostic group when that drug may be prescribed by a general practitioner without the help of specialized diagnostic equipment. Our data have demonstrated the efficacy of temazepam for what now must be termed a highly selected patient population. It is now being recommended by sleep researchers that future

evaluations of a potential hypnotic in a sleep laboratory use a different patient selection process. Thus, more information on the safety and efficacy of the drug may be obtained for disorders that present with the complaint of insomnia but are organic in nature, such as nocturnal myoclonus, diaphragmatic sleep apnea and the dyssomnias associated with disruptions of the 24-h sleep–wake cycle.

References

DEMENT, W.C., CARSKADON, M.A., MITLER, M.M., PHILLIPS, R.L. & ZARCONE, V.P. (1978). Prolonged use of flurazepam: A sleep laboratory study. *Behav. Med.*, **5**, 25-31.

FEINBERG, J., FEIN, G., WALKER, J., PRICE, J., PRICE, L., FLOYD, T. & MARCH, J. (1977). Flurazepam effects on slow-wave sleep: Stage 4 suppressed but number of delta waves constant. *Science,* **198**, 847-849.

GAMES, P.A. (1977). An improved *t*-table for simultaneous control on *g* contrasts. *J. Am. Stat. Assoc.*, **72**, 531-537.

HUYNH, H. (1978). Some approximate tests for repeated measurement designs. *Psychometrika,* **43**, 161-175.

KALES, J.D., BIXLER, E.O., SLYE, E.I. & KALES, A. (1971). Effects of placebo and flurazepam on sleep patterns in insomniacs. *Clin. Pharmac. Ther.*, **12**, 691-697.

KALES, A., KALES, J., BIXLER, E. & SCHARF, M. (1975). Effectiveness of hypnotic drugs with prolonged use. *Clin. Pharmac. Ther.*, **13**, 356-363.

KALES, A., SCHARF, M. & KALES, J. (1978). Rebound insomnia: A new clinical syndrome. *Science,* **201**, 1039-1040.

RECHTSCHAFFEN, A. & KALES, A. (ed.) (1968). *A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects.* Public Health Service Publication No. 204. Washington, DC: US Government Printing Office.

WINER, B.J. (1962). *Statistical Principles in Experimental Design.* New York: McGraw-Hill.