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EFFECT OF THE 1,5-BENZODIAZEPINES, CLOBAZAM AND TRIFLUBAZAM, ON SLEEP IN MAN

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1 The effect of the 1,5-benzodiazepines, clobazam (10 and 20 mg) and triflubazam (20 and 40 mg), on sleep was studied in six healthy males using electroencephalography for sleep measures and analogue scales for subjective assessments of well being and sleep quality. The effect of clobazam was limited to the night of ingestion. There was some evidence from subjective assessments that the effect of triflubazam may have persisted beyond the night of ingestion.

2 No effect of clobazam or triflubazam was observed on total sleep time, stage shifts in the first 6 h or latency to the first rapid eye movement period of sleep. With clobazam sleep onset latency was shortened ($P < 0.05$), but this effect was not seen with triflubazam. The latency to stage 3 was shortened by both drugs. There was evidence of reduced duration of awake (stage 0) activity and drowsy (stage 1) sleep with both drugs.

3 The percentage stage 1 sleep was reduced by clobazam (10 and 20 mg) and by triflubazam (20 mg) ($P < 0.05$), though the effect was not significant with triflubazam (40 mg). Clobazam (20 mg) increased the percentage stage 2 sleep ($P < 0.05$), but reduced the percentage stage 3 ($P < 0.01$) and stages 3 + 4 ($P < 0.05$) sleep. There were no other effects on percentage of total sleep time occupied by various sleep stages or in duration (min) of sleep stages, except that the duration (min) of stage 2 sleep in the second 2 h interval of sleep was increased with clobazam (20 mg) ($P < 0.01$).

4 Subjects reported impaired sleep with triflubazam (40 mg) ($P < 0.05$), and a sense of less wakefulness the morning after ingestion of clobazam (10 and 20 mg) ($P < 0.01$) and triflubazam (40 mg) ($P < 0.05$).

Introduction

Many benzodiazepines with hypnotic properties have residual effects during the day after overnight ingestion (Bond & Lader, 1972, 1973 & 1975; Borland & Nicholson, 1975a), but the 1,4-benzodiazepine, diazepam, and the 1,5-benzodiazepine, clobazam, have less persistent sequelae (Caille & Bassano, 1974; Borland & Nicholson, 1975b). In previous studies we have examined the effects of diazepam, its principal metabolites, N-desmethyldiazepam (nordiazepam) and 3-hydroxydiazepam (temazepam), and other closely related benzodiazepines on sleep in man (Nicholson & Stone, 1976; Nicholson, Stone & Clarke, 1976; Nicholson, Stone, Clarke & Ferres, 1976), and it would appear that diazepam, or a closely related drug, may prove to be useful in the management of disturbed sleep and be appropriate for persons involved in skilled activity. In this context the limited effect on performance of clobazam raises the possibility that the 1,5-benzodiazepines, as a group, may be useful in the management of disturbed sleep when impaired performance the next day is unacceptable, and so we have investigated the effect of clobazam (7-chloro-1-methyl-5-phenyl-1,5-benzodiazepine-2,4 dione) and a closely related drug, triflubazam (7-trifluoromethyl-1-methyl-5-phenyl-1,5-benzodiazepine-2,4 dione), on sleep in healthy man (Figure 1).

Methods

The subjects were six healthy male volunteers aged between 21 and 28 years. They were familiar with the sleep laboratory and with the techniques used in recording sleep activity. The assessment of each treatment (placebo or dose of a drug) involved four days. For two nights the subjects slept at home and retired at a set time between 23.00 and 23 h 30 min, and for the next two nights the subjects slept in the sleep laboratory. They were required to refrain from napping and undue exercise, and to abstain from caffeine and alcohol after mid-day on the days which involved recordings. The sleep laboratory was sound attenuated, and the temperature (18 ± 1°C) and humidity (55 ± 2%) were controlled. Nine to twelve days separated each assessment.

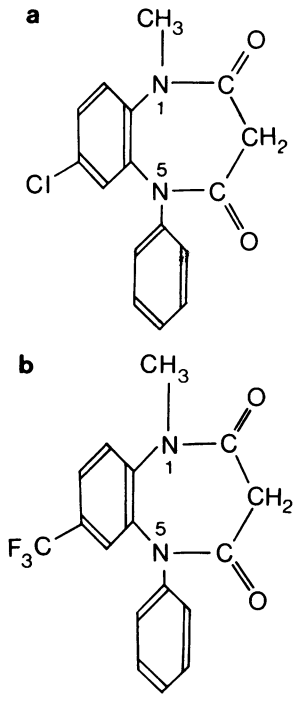

Figure 1 Structural formulae of the 1,5-benzodiazepines, (a) clobazam and (b) triflubazam.

The subjects reported at the sleep laboratory 1.5 h before their set time to retire. At 0.5 h before lights out the subjects completed assessments of their well-being related to a 100 mm analogue scale. The assessments were A: How did you feel during the day? and B: How do you feel now? The extremes of the scales were tired (00)/fresh (100) and very tired (00)/wide awake (100) respectively. The drug or placebo was ingested on the third night only (first night in the laboratory) and was taken with water at the set time between 23.00 and 23 h 30 min (lights out). No capsules were ingested on the fourth night (second night in the laboratory) and this night (recovery night) was used to observe any residual effects of the drugs. Each subject received two ingestions of placebo (each a separate 4 day assessment), clobazam (10 and 20 mg) and triflubazam (20 and 40 mg) in a random schedule. The placebo was identical in appearance to the drugs, and the study was double blind.

In the morning the subjects were allowed to wake naturally, and 0.5 h after awakening completed four further assessments. The assessments and the extremes of the 100 mm analogue scales were C: I slept *very poorly – very well*; D: Now I feel *very sleepy – wide awake*; E: I fell asleep *never – immediately* and F: After I fell asleep I slept *very badly – very well.* In each case a favourable response tended toward the 100 extreme of the scale.

Details of recording techniques, scoring of the electroencephalographic (eeg) records and sleep stages, and statistical analysis of sleep measures and analogue scales are given in a previous paper (Nicholson, Stone, Clarke & Ferres, 1976).

Results

Studies with the two ingestions of placebo revealed no differences between the sleep measures, and so they were combined to form the control values. No effect of clobazam (10 and 20 mg) and triflubazam (20 and 40 mg) was observed on total sleep time, stage shifts

Table 1 Effect of clobazam (10 mg and 20 mg) and triflubazam (20 mg and 40 mg) on various sleep measures (means for six subjects)

		Night of ingestion					*Recovery night*				
			Clobazam (mg)		*Triflubazam (mg)*			*Clobazam (mg)*		*Triflubazam (mg)*	
Measure	*C/V*	*Placebo*	*10*	*20*	*20*	*40*	*Placebo*	*10*	*20*	*20*	*40*
Total sleep time (min)	7	420.4	459.5	441.1	439.6	410.2	454.4	448.1	448.8	430.5	431.8
Stage shifts in first 6 h	22	54.8	49.5	49.7	48.5	59.8	58.0	47.3	48.5	57.8	55.2
Sleep onset latency (min)	40	27.1	17.7*	16.0*	26.3	25.8	20.7	19.1	22.3	22.0	22.3
Latency (min) to stage 3	29	18.2	13.8	16.2	14.5	14.6	14.0	19.6	17.4	13.8	20.0
Latency (min) to stage REM	40	99.4	114.2	134.2	103.0	68.4	80.2	88.2	82.2	80.9	80.8
REM/NREM ratio	13	0.33	0.34	0.34	0.36	0.36	0.38	0.40	0.41	0.34	0.38

Coefficient of variability (C/V) = s.d. × 100/mean.
Significance level: * = 5%.

in first 6 h, latency to the first rapid eye movement period of sleep, and the ratio of the duration of rapid eye movement (REM) and non rapid eye movement (NREM) sleep (Table 1). With clobazam (10 mg and 20 mg) sleep onset latency was shortened ($P < 0.05$), but this effect was not observed with triflubazam.

The means for sleep onset latency and latency to stage 3 sleep are given in Table 1. The data were also tested against the hypothesis that the observations were distributed equally around critical values (Table 2). For sleep onset latency the values chosen were 25 and 30 minutes. With placebo and triflubazam the hypothesis was supported for each value, but with clobazam it was rejected at the 30 min latency ($P < 0.001$). For latency to stage 3 activity the values chosen were 20 and 25 minutes. With placebo the hypothesis was supported for each value, but with clobazam and triflubazam it was rejected at the 25 min latency ($P < 0.001$ and < 0.05 respectively).

Table 2 Levels of significance for deviation from equal distribution around critical values for latency (min) to sleep stages 2 (sleep onset latency) and 3 for night of ingestion with placebo, clobazam and triflubazam

Sleep stage	2		3	
Critical times (min)	25	30	20	25
Placebo	NS	NS	NS	NS
Clobazam	NS	***	NS	***
Triflubazam	NS	NS	NS	*

Significance levels: *=5%; ***=0.1%; NS=Not significant

The analysis of awakenings is given in Tables 3 and 4. For number of awakenings to stage 0 and stage 1 activity the critical values were 9, 12 and 15, and 6, 9 and 12 respectively. There were no effects of clobazam and triflubazam on number of awakenings to stage 0, but there was an effect of triflubazam on number of awakenings to stage 1 activity. For duration of awakenings to stage 0 and stage 1 activity the critical values were 20, 25 and 30 min and 6, 9 and 12 min respectively. There was an effect of clobazam and triflubazam on duration of awakenings to both stage 0 and stage 1 activity.

The effect of clobazam and triflubazam on the percentage of total sleep time occupied by each sleep stage is given in Table 5. Stage 1 activity was reduced by clobazam (10 mg and 20 mg) and by triflubazam (20 mg) ($P < 0.05$), though this latter effect was not seen with 40 mg triflubazam. Clobazam (20 mg) increased the percentage of total sleep time occupied by stage 2, but reduced the percentage of total sleep

Table 3 Effect of clobazam and triflubazam on number and duration (min) of awakenings during the first 6 h of sleep for the night of ingestion (means for six subjects)

Awakening (sleep stage)	*Measure*	*C/V*	*Placebo*	*Clobazam (mg)* 10	20	*Triflubazam (mg)* 20	40
0	Number	40	7.3	6.8	6.8	7.3	8.3
	Duration (min)	97	29.4	16.3	19.6	16.1	38.3
1	Number	46	5.8	6.2	4.8	3.8	4.2
	Duration (min)	48	4.9	4.9	4.0	3.1	3.0

Coefficient of variability (C/V) = s.d. × 100/mean.

Table 4 Levels of significance for deviation from equal distribution around critical values for number and duration (min) of awakenings during first 6 h of night of ingestion with placebo, clobazam and triflubazam

Awakening (sleep stage)	*Treatment*	*Number*			*Duration (min)*		
		<9	*<12*	*<15*	*<20*	*<25*	*<30*
0	Placebo	NS	*	***	NS	NS	NS
	Clobazam	NS	**	**	NS	NS	*
	Triflubazam	NS	**	***	NS	NS	*
		<6	*<9*	*<12*	*<6*	*<9*	*<12*
1	Placebo	NS	*	***	NS	*	***
	Clobazam	NS	**	**	**	**	**
	Triflubazam	*	***	***	**	***	***

Significance levels: *=5%; **=1%; ***=0.1%; NS=Not significant

time occupied by stage 3 and by the stages 3 + 4. There were no other effects on the night of ingestion, and there were no effects on the recovery night. The effect of the drugs on the duration (min) of sleep stages is given in Table 6. No effects of clobazam (10 and 20 mg) and triflubazam (20 and 40 mg) were observed during the night of ingestion or during the recovery night. However, an analysis of 2 hourly intervals of sleep from sleep onset latency (Table 7) revealed an increase in the duration of stage 2 activity during the second interval with clobazam (20 mg) ($P < 0.01$).

Assessments by the subjects are given in Table 8. There were no changes in assessments of sleep except with triflubazam (40 mg). The subjects as a group reported impaired sleep (assessment F) during the night of ingestion ($P < 0.05$). The assessments revealed less wakefulness in the morning (assessment D) after ingestion of clobazam (10 and 20 mg) ($P < 0.01$) and

Table 5 Effect of clobazam (10 mg and 20 mg) and triflubazam (20 mg and 40 mg) on percentage of total sleep time occupied by each sleep stage (means for six subjects)

		Night of ingestion					*Recovery night*				
			Clobazam (mg)		*Triflubazam (mg)*			*Clobazam (mg)*		*Triflubazam (mg)*	
Sleep stage	*C/V*	*Placebo*	*10*	*20*	*20*	*40*	*Placebo*	*10*	*20*	*20*	*40*
1	32	6.6	4.4*	4.3*	4.4*	6.4	5.5	4.6	4.9	5.2	5.0
2	8	49.2	51.9	54.7*	49.7	49.2	49.2	50.9	51.1	49.4	52.1
3	19	11.2	10.7	7.7**	11.2	12.2	10.5	9.8	10.5	13.2	9.8
3 + 4	16	19.7	18.5	16.3*	19.2	18.5	18.0	16.4	15.1	20.3	16.0
REM	10	24.6	25.3	24.7	26.6	26.0	27.4	28.1	28.9	25.2	26.9

Coefficient of variability (C/V) = s.d. × 100/mean.
Significance levels: * = 5%; ** = 1%.

Table 6 Effect of clobazam (10 mg and 20 mg) and triflubazam (20 mg and 40 mg) on duration (min) of sleep stages in first 6 h of sleep (means for six subjects)

		Night of ingestion					*Recovery night*				
			Clobazam (mg)		*Triflubazam (mg)*			*Clobazam (mg)*		*Triflubazam (mg)*	
Sleep stage	*C/V*	*Placebo*	*10*	*20*	*20*	*40*	*Placebo*	*10*	*20*	*20*	*40*
0	124	19.8	10.8	15.5	9.6	26.5	9.8	8.7	5.7	7.7	9.3
1	37	15.9	11.7	11.1	11.6	16.8	16.7	12.3	13.9	15.0	14.3
2	104	169.7	179.2	195.6	171.6	165.0	176.1	184.3	193.4	176.2	188.5
3	26	46.4	47.3	35.0	50.3	49.1	41.9	44.5	47.4	54.4	40.6
3 + 4	17	81.9	83.6	74.7	87.9	74.8	77.5	75.1	68.4	83.4	67.4
REM	18	72.9	74.8	63.2	79.3	76.8	80.0	79.7	78.5	77.8	80.6

Coefficient of variability (C/V) = s.d. × 100/mean.

Table 7 Effect of clobazam (10 and 20 mg) and triflubazam (20 mg and 40 mg) on 2 hourly distribution (min) of sleep stage 2 from sleep onset latency (means for six subjects)

		Night of ingestion					*Recovery night*				
			Clobazam (mg)		*Triflubazam (mg)*			*Clobazam (mg)*		*Triflubazam (mg)*	
Interval (h)	*C/V*	*Placebo*	*10*	*20*	*20*	*40*	*Placebo*	*10*	*20*	*20*	*40*
0–2	20	52.9	52.5	45.4	57.9	53.7	51.6	54.9	64.7	53.6	60.1
2–4	16	56.0	61.9	76.8**	59.9	62.3	58.1	67.7	59.5	64.5	64.2
4–6	21	60.9	64.8	73.3	53.8	49.0	66.4	61.7	69.3	58.1	64.3

Coefficient of variability (C/V) = s.d. × 100/mean.
Significance levels: ** = 1%.

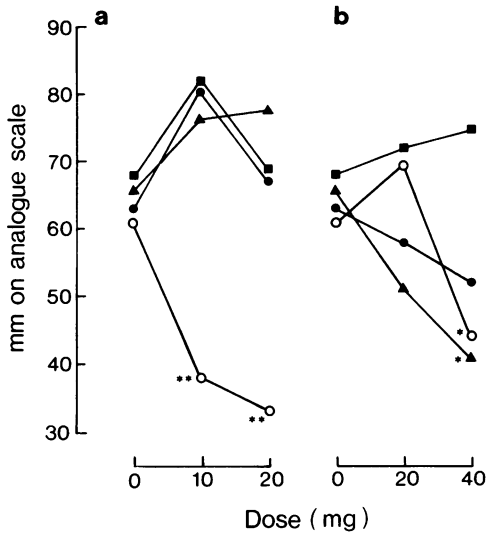

Figure 2 Subjective assessments of sleep quality (C=●; D=■; F=▲) and well-being (D=○) after overnight ingestion of (a) clobazam and (b) triflubazam. For explanation of assessments see text (*=5%; **=1%).

triflubazam (40 mg) ($P<0.05$), and the effect with triflubazam was seen the morning after the recovery night (Figure 2).

A regression analysis was carried out between the subjective assessments and the eeg measures of sleep. Mean values (subjective assessments and eeg measures) were subtracted from the individual subject values, and the change from the mean used in the analysis. This eliminated the drug effect, but reduced the degrees of freedom of the residuals. It was not possible to show relations between the EEG measures and assessments of well being (A, B & D), but with assessments of sleep (C, E & F) relations were established. With assessment C (overall sleep) dependence was found with duration (min) of awake (stage 0) activity (negative), stage 3 (positive) and stage REM (negative) sleep using a partial F test. With assessment E (falling asleep) a positive dependence was found, as expected, for sleep onset latency ($P<0.01$, t-test), and for the remaining EEG measures a partial F test showed a positive dependence with duration (min) stage 3 sleep ($P<0.01$, t-test). With assessment F (staying asleep) dependence was established with duration of stage 1 (positive) and stage 3) (positive) sleep and awakenings 0+1 (negative) ($P<0.01$, t-test).

Discussion

It is evident from these studies that the 1,5-benzodiazepines have less effect on sleep than the 1,4-benzodiazepines. The hypnotic activity of triflubazam (20 mg) is minimal, and, though clobazam (10–20 mg) shortens sleep onset latencies and reduces awake and drowsy activity, total sleep time is not increased. However, it is the limited, though useful, effects of clobazam which may prove to be appropriate in the management of disturbed sleep. In a previous study it was not possible to establish unequivocally even immediate effects of clobazam on performance (Borland & Nicholson, 1975b), and, even though the subjects reported impaired wakefulness during the morning after ingestion, it would appear that the adverse assessments are unlikely to be related to changes in performance. The overnight ingestion of clobazam would not lead to the residual sequelae observed with some of the 1,4-benzodiazepines (Bond & Lader, 1972, 1973; Borland & Nicholson, 1975a), and so it may prove particularly useful for persons involved in skilled activity.

Table 8 Effect of clobazam (10 mg and 20 mg) and triflubazam (20 mg and 40 mg) on assessments of well-being and sleep quality (means for six subjects). The data refer to mm on a 100 mm scale

Assessment	C/V	Placebo	Clobazam (mg) 10	Clobazam (mg) 20	Triflubazam (mg) 20	Triflubazam (mg) 40	Placebo	Clobazam (mg) 10	Clobazam (mg) 20	Triflubazam (mg) 20	Triflubazam (mg) 40
			Night of ingestion					*Recovery night*			
A	30	58.4	51.4	60.8	57.0	53.4	51.0	63.6	72.2	75.2	60.4
B	49	41.0	21.0	37.8	42.0	43.2	30.2	43.8	47.4	39.2	33.6
			Morning after ingestion					*Morning after recovery night*			
C	22	63.2	81.0	67.4	58.8	52.2	66.2	73.8	64.8	66.6	61.0
D	21	61.2	37.8**	33.2**	69.4	44.0*	64.8	54.6	65.0	71.8	44.2*
E	14	67.8	81.0	78.4	71.8	74.4	65.8	78.4	73.8	71.4	82.0
F	22	66.2	76.6	77.4	51.4	40.6*	70.4	77.8	66.4	75.6	61.4

Coefficient of variability (C/V) = s.d. × 100/mean.
Significance levels: *=5%; **=1%.

These and the previous studies suggest that diazepam (5–10 mg) and clobazam (10–20 mg) are promising drugs for the management of disturbed sleep when impaired performance the next day would be unacceptable. However, the *repeated* use of diazepam may lead to residual effects because of its long acting metabolite, nordiazepam, and the adverse assessments of well being the morning after ingestion of clobazam may influence acceptability. The effects of nordiazepam on performance are uncertain (Tansella, Zimmerman-Tansella & Lader, 1974; Palva & Linnoila, 1975, (unpublished observations); Borland & Nicholson, 1977), though it is likely that psychomotor impairment may be minimal, and may be overcome by increased effort. With clobazam it is difficult to reconcile the adverse assessments after overnight ingestion with the observations on sleep and on performance, and so the assessments may not be a consistent effect and may not be of clinical importance.

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