EFFICACY OF SOME BENZODIAZEPINES FOR DAY-TIME SLEEP

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- 1 Effects of flunitrazepam (0.25–0.50 mg) and the 1,4-triazolodiazepines, triazolam (0.25–0.50 mg) and brotizolam (0.3–0.6 mg), on day time sleep were studied by electroencephalography.
- 2 Flunitrazepam (0.25–0.50 mg) and triazolam (0.25–0.50 mg) reduced awake activity ($P < 0.05$) and improved the sleep efficiency index ($P < 0.05$). The higher dose of each drug increased total sleep time ($P < 0.05$ and < 0.01 respectively) and duration of stage 2 sleep ($P < 0.01$), and also delayed the first REM period ($P < 0.05$ and < 0.01 respectively).
- 3 Brotizolam (0.6 mg) markedly increased total sleep time ($P < 0.001$) and the sleep efficiency index ($P < 0.01$), and prolonged stage 2 ($P < 0.01$) and slow wave ($P < 0.01$) sleep. Over the dose range 0.3–0.6 mg, the latency to stage 3 sleep was shortened ($P < 0.05$), and that to the first REM period lengthened ($P < 0.05$).
- 4 All three drugs improved day time sleep. However the present observations and data from previous studies suggest that flunitrazepam (0.25–0.50 mg) may be particularly appropriate for sleep at unusual times.

Introduction

Although the sleep disturbance associated with shift-work has been well documented, little attention has been paid to the choice of an hypnotic for use at unusual times. Previously (Nicholson & Stone, 1979) we studied diazepam and its hydroxylated metabolites, temazepam and oxazepam, and showed that, though their effectiveness for afternoon sleep varied, it did not relate to their night time activity. Diazepam was effective in both situations, whereas temazepam and oxazepam were less active during the day than at night.

It would appear that usefulness for nocturnal sleep may not be an indication of potential for sleep at other times of the day. A day time sedative must be effective when the circadian desire for sleep may be less, and its activity during the first few hours is crucial. Further, as day time rest tends to be shorter than night time sleep, a limited duration of action without residual impairment is desirable. Relatively rapid kinetics may be essential to meet these conditions, and so we have studied three drugs, the 1,4-benzodiazepine, flunitrazepam, and the 1,4-triazolodiazepines, triazolam and brotizolam, which may fulfil this requirement.

Methods

The subjects were six healthy male volunteers aged between 18 and 28 years. Their sleep patterns were

normal, and they were familiar with the laboratory and sleep recording, and were not taking any other medication. On the previous night they avoided alcohol and retired at a set time between 23.00 and 23.30 h. They were also required to refrain from napping and undue exercise, and to abstain from caffeine and alcohol on the experimental day. The sleep laboratory was sound attenuated, and the temperature and humidity were controlled.

Three channels of electroencephalography (EEG) were recorded from the C_4-A_1 , P_1-T_5 and $O_2-P_2-O_3$ positions. Silver-silver chloride disc electrodes were fixed with collodion and the scalp abraded to obtain resistances which did not exceed 10 Kohms. The submental electromyogram (EMG) and the right and left electro-oculograms (EOG) were also recorded. A Grass 8–10 EEG machine was used, situated in an adjoining room. The paper was run at a speed of 10 mm s⁻¹. The half amplitude frequency response was 0.1–35 Hz for the EEG, 2.0–70 Hz with a selective 50 Hz notch filter for the EMG, and 1.0–15 Hz for the EOG.

The records were scored independently into 30 sec epochs by two analysts according to the scheme of Rechtschaffen & Kales (1968). Differences in the annotation of sleep stages were resolved, but did not occur in more than 4% of periods. The sleep stage data was analysed for various measures and comparisons between placebo and verum sleep were made. The coefficient of variability (s.d. $\times$ 100/mean) of each measure (C/V) was used as a preliminary criterion to decide whether an analysis of variance

was appropriate. The arbitrary level was 50%, and if the value was above 50% the Friedman two-way analysis of variance was used.

Each experiment involved one afternoon, separated by at least 7 days. The subjects had slept at home on the preceding night, and reported to the laboratory at 12.30 h when a light lunch was provided. In the first week a placebo ingestion allowed adaptation to the environment. Each subject was given on separate occasions 10 mg diazepam, 0.25 and 0.50 mg flunitrazepam, 0.25 and 0.50 mg triazolam, 0.30 and 0.60 mg brotizolam, and two further placebos. A multiple dummy technique was used with treatments arranged in a random order. The doses were chosen with reference to previous night time studies (Nicholson & Stone, 1980; Nicholson, Stone & Pascoe, 1980). Subjects retired to bed at 14.00 h and took identical capsules with water. The bedroom lights were then switched off, and recordings began immediately. They were allowed to get up at 20.00 h. Night time sleep after placebo was also recorded, and the subjects were left to wake naturally in the morning though only the sleep of 6 hours from 'lights out' was used in the analysis.

Results

The results are given in Tables 1, 2, 3 and 4. Day time sleep after drugs and night time sleep after placebo are compared statistically with day time sleep after placebo. The higher dose of each drug, together with 10 mg diazepam, lengthened total sleep time and increased the duration of stage 2 sleep. Flunitrazepam (0.25–0.50 mg) and triazolam (0.25–0.50 mg) reduced awake activity, and brotizolam showed a similar trend. Each drug reduced the latency to stage 3 sleep and delayed the first REM period, though the duration of REM sleep was not changed. Triazolam (0.50 mg) and brotizolam (0.60 mg) prolonged the time spent in slow wave sleep. The sleep efficiency index was improved by all four drugs. The cumulated sleep times related to hourly intervals from 'lights out' are given in Table 4.

Discussion

Previously we suggested that diazepam, in doses up to but not exceeding 10 mg, would be a useful day time sedative (Nicholson & Stone, 1979; Stone, 1979), and the present study supports this recommendation. Diazepam (10 mg) reduces awake activity and improves the efficiency of day time sleep, at this dose it is unlikely to impair performance beyond a few hours after ingestion (Clarke & Nicholson, 1978). This relatively short duration of action is almost certainly related to its pharmacokinetic profile, in which an opti-

mum relationship exists between the α and β phase kinetics. Either the α phase has a short half life and plays a significant part in the fall of plasma level, or the half lives of the α and β phases together lead to a sustained fall. It would appear that rapid recovery from the effects of a single ingestion of diazepam is likely to be related to its short distribution half life of around 2 h.

On the other hand with daily ingestion, the prolonged elimination half lives of diazepam (Mandelli, Tognoni & Garattini, 1978) and of its metabolite, nordiazepam (Post, Lindgren, Bertler & Malmgren, 1977), are likely to lead to accumulation with persistent effects on performance and behaviour. Nevertheless there are hypnotics which may be used nightly when residual sequelae are to be avoided. Temazepam (20 mg) and triazolam (0.25 mg) are appropriate, and brotizolam (0.2–0.3 mg) may prove equally useful (Nicholson & Stone, 1976; Clarke & Nicholson, 1978; Nicholson *et al.*, 1980).

However, these benzodiazepines are less suitable for day time sleep when effectiveness during the first hour or so after ingestion together with limited persistence of activity are crucial. Recovery from temazepam (20 mg) is rapid, but it has less hypnotic effect than diazepam (10 mg), and, though the effects of triazolam (0.25 mg) and brotizolam (0.2–0.3 mg) on sleep in the afternoon are similar to diazepam (10 mg), previous studies on performance after day time ingestion suggest that residual impairments are likely after a relatively short period of day time rest (Nicholson & Stone, 1980; Nicholson *et al.*, 1980).

Flunitrazepam, on the other hand, may prove to be particularly useful for sleep at unusual times. There is only a transient impairment of performance after the morning ingestion of 0.25 mg (Nicholson & Stone, 1980), and its sleep inducing effects during the day are similar to equal doses of triazolam and brotizolam. Further, there are no residual sequelae after overnight ingestion of 0.5 mg, and so impairments are unlikely to persist beyond a few hours, and, at this dose, flunitrazepam is at least as good for afternoon sleep as 10 mg diazepam. Amrein, Cano, Hartmann, Ziegler & Dubuis (1979) have suggested that the relatively short duration of the sleep inducing effect of flunitrazepam during the day is related to its plasma concentration profile, and in this way it may resemble diazepam. There is a rapid fall in plasma concentration, but this is due only to a small extent to the elimination processes reflected in β phase kinetics with a half life of around 20 h. The distribution phase into the deep compartment is responsible for the immediate fall in plasma level, and this is estimated to have a half life of 3–4 h.

Though flunitrazepam is an effective and rapidly absorbed hypnotic, doses of 1 mg and above have residual effects (Bond & Lader, 1975), depress slow wave sleep, reduce REM sleep during the early part

Table 1 Effect of drugs on various sleep measures of day-time sleep (means for six subjects)

Measure (min)	C/V	Placebo		Diazepam (mg) 10	Flunitrazepam (mg)		Triazolam (mg)		Brotizolam (mg)	
		Night-time sleep	Day-time sleep ¹		0.25	0.50	0.25	0.50	0.30	0.60
Total sleep time	22.4	325.6 ***	167.5	229.9	207.3	241.5 *	212.3	272.2 **	210.3	289.7 ***
Sleep onset latency	42.6	26.3	23.0	13.2	20.1	16.2	18.7	25.9	22.0	17.4
Latency to stage 3	39.8	13.3 **	29.7	26.5	19.3 *	24.0	18.8 *	19.0	17.7 *	20.7 (*)
Latency to stage REM	35.5	88.9 **	43.6	67.0	46.3 *	72.8	65.6	88.4 **	74.2 *	70.8 (*)
² Sleep efficiency index	9.5	0.90 **	0.76	0.90 *	0.86 *	0.89 *	0.87 *	0.87 *	0.80	0.92 **

C/V Coefficient of variability (s.d. $\times$ 100/mean) of each measure.Significance levels: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.¹ Statistical comparisons are with day time sleep after placebo.² Sleep efficiency index = Total sleep time/time in bed.**Table 2** Effect of drugs on the duration (min) of sleep stages of day-time sleep (means for six subjects)

Sleep stage	C/V	Placebo		Diazepam (mg) 10	Flunitrazepam (mg)		Triazolam (mg)		Brotizolam (mg)	
		Night-time sleep	Day-time sleep ¹		0.25	0.50	0.25	0.50	0.30	0.60
² Awake	88.4	8.2	14.2	4.6 *	8.5 *	7.0	3.8 *	5.6	4.7	3.8
1	48.1	19.1	21.0	13.0	12.7	13.1	13.5	15.1	17.1	13.3
2	27.0	181.6 ***	88.1	136.3 *	121.3	150.6 **	115.4	163.8 **	115.7	165.2 **
3	45.1	40.2 **	19.2	32.8	21.8	23.4	28.3	29.9	28.0	42.6 **
4	94.7	24.6	10.7	3.0	8.5	8.5	11.8	20.3	17.7	18.8
3+4	42.4	64.8 **	29.9	35.8	30.3	31.9	40.1	50.2 (*)	45.7 **	61.3 **
REM	39.5	60.2 *	40.8	51.3	49.3	53.8	47.8	50.8	40.8	54.3

C/V Coefficient of variability (s.d. $\times$ 100/mean) of each measure.Significance levels: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.¹ Statistical comparisons are with day time sleep after placebo.² Non-parametric analysis.

Table 3 Effect of drugs on the percentage occupied by each sleep stage of day-time sleep (means for six subjects)

Sleep stage	C/V	Placebo					Triazolam (mg) 0.25 0.50	Brotizolam (mg) 0.30 0.60
		Night-time sleep	Day-time sleep ¹	Diazepam (mg) 10	Flunitrazepam (mg) 0.25 0.50	Triazolam (mg) 0.25 0.50		
² Awake	103.5	2.5	7.9	1.8 *	3.8 *	1.8 *	3.8	1.3
1	61.7	5.9	11.8	5.5	5.7	6.3	10.3	4.6
2	12.2	55.8	48.9	57.1	56.0	52.8	58.7	55.7
3	40.5	12.3	10.8	14.1	10.8	14.1	10.7	14.6
4	76.8	7.6	7.0	1.1	4.4	4.6	7.2	6.9
3+4	38.5	19.9	17.9	15.3	15.1	18.7	17.9	21.5
REM	25.5	19.3	21.4	22.1	23.1	22.1	17.8	18.0

C/V Coefficient of variability (s.d. $\times$ 100/mean) of each measure.Significance levels: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.¹ Statistical comparisons are with day time sleep after placebo.² Non-parametric analysis.**Table 4** Effect of drugs on cumulated sleep time (min) related to hourly intervals from 'lights out'

Time (h) from 'lights out'	Placebo					Triazolam (mg) 0.25 0.50	Brotizolam (mg) 0.30 0.60
	Night-time sleep	Day-time sleep ¹	Diazepam (mg) 10	Flunitrazepam (mg) 0.25 0.50	Triazolam (mg) 0.25 0.50		
1	33.0	33.3	45.0	38.3	39.1	35.6	40.9
2	88.8	76.2	102.3 ***	92.8 *	96.7 **	92.4 *	99.4 **
3	145.6 *(*)	117.0	149.8 **	145.6 **	149.3 **	148.7 **	155.8 ***
4	199.9 **	149.3	193.2 *	184.8 *	177.8 **	197.8 **	211.4 ***
5	254.3 ***	159.1	213.0 *	196.3 *	196.3 **	240.8 **	262.8 ***
6	306.5 ***	159.1	222.8 *	200.8 *	203.2 **	264.0 **	282.2 ***

These values include the period covered by the sleep onset latency but exclude stage 1 (drowsy) sleep.

¹ Statistical comparisons are with day time sleep after placebo.

of the night and possibly lead to unpleasant and emotional dreams (Monti & Allier, 1973; Jovanović, 1977; Gaillard & Phellipeau, 1977). However, 0.25–0.50 mg flunitrazepam decreases awake activity and drowsy sleep without altering the duration of REM and slow wave sleep (Nicholson & Stone, 1980), and with 0.75 mg slow wave or REM sleep are still not reduced (Nicholson & Stone—unpublished data).

These observations suggest that flunitrazepam in doses around 0.5 mg, is a useful hypnotic, though further dose and time response studies related to its pharmacokinetic profile are needed to establish its usefulness for sleep at unusual times.

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