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MIDAZOLAM: SLEEP AND PERFORMANCE STUDIES IN MIDDLE AGE

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1 Effects of 10, 20 and 30 mg midazolam on sleep and on performance the next day were studied in six healthy adult males aged between 47 and 53 years. The study was double-blind, placebo-controlled and included another rapidly eliminated benzodiazepine (brotizolam, 0.25 mg) as an active control.

2 With 10 mg midazolam, sleep-onset latency was quicker, and the duration and percentage of stage 2 sleep was increased over the first 6 h. Effects of 20 and 30 mg midazolam were similar to each other. Sleep onsets were earlier, total sleep times and stage 2 sleep were increased, and the sleep efficiency indices improved. During the first 6 h there was reduced duration and percentage of drowsy (stage 1) sleep.

3 There was no consistent evidence of delay to the first period of rapid eye movement sleep, but over the dose range the duration was reduced during the first 2 h.

4 Digit symbol substitution did not show any residual decrement 9 h after ingestion of 10, 20 or 30 mg midazolam.

5 Midazolam may prove to be a particularly useful hypnotic for shiftworkers whose rest periods tend to be shorter than in those who have a regular nocturnal sleep pattern.

Introduction

Hypnotics with rapid elimination may be useful for those involved in skilled activity, and there are several available or under investigation. However, elimination is not the only factor which determines the duration of action of an hypnotic (Amrein *et al.*, 1983); the rate of absorption and of fall in plasma level during the distribution phase are also important. In this context midazolam, an imidazobenzodiazepine, has a very rapid elimination and this, together with fast absorption and distribution, suggests that it may be particularly short-acting (Heizemann *et al.*, 1983). Indeed, the hypnotic activity of midazolam in young healthy adults is limited to the early hours of the night, and it provides a dose range—from 10 to possibly 30 mg—free of performance decrements the next day (Nicholson & Stone, 1982).

Clearly, midazolam is potentially useful for those, such as shiftworkers, whose periods of rest may be relatively short. However, we have reported (Nicholson *et al.*, 1982) that in the middle-aged a somewhat wider dose range than that needed by young adults may be necessary to ensure an adequate effect of an hypnotic, and it is in this context that we have carried out a further study with midazolam in older subjects.

Methods

Six healthy male volunteers aged between 47 and 53 (mean 49) years were studied. They were required to avoid napping and undue exercise, and to abstain from alcohol on the day before and on each experimental day. No beverages containing caffeine were consumed from mid-day until after the performance session the next morning. Two adaptation nights when placebos were ingested were separated by 1 week. Each subject then received 0.25 mg brotizolam as the active control, 10, 20 and 30 mg midazolam, and two further placebos. A multiple dummy technique was used, and the treatments were arranged double-blind in a pseudo-random order to avoid undue bias, with a week separating each ingestion. Tablets were taken under supervision at 'lights out' (2300 or 2330 h) which was fixed for each subject. The treatments and placebo ingestions were distributed evenly over the experiment.

Two groups of three subjects who reported 1.5 h before bedtime, slept in individual light-proofed, sound-attenuated and temperature (18 ± 1°C) and humidity (55 ± 1%) controlled rooms. In an adjoining room three channels of electroencephalographic (EEG) activity were recorded (C4–A1,

P1–T5, and OzPz–03), together with eye movements and the submental electromyogram using a paper speed of 10 mm s^{-1}. Additional details of recording techniques are given elsewhere (Nicholson *et al.*, 1982). The subjects were awoken, if necessary, at the same time each week (0715 or 0730 h). Each sleep record was scored independently into 30-s epochs by two analysts according to the criteria of Rechtschaffen & Kales (1968), and disagreements (which did not occur in more than 4% of the epochs) resolved.

Assessments of sleep and well-being on a 100 mm analogue scale were completed 0.5 h after awakening. The assessments and extremes of the scale were: 'I slept, *very poorly–very well*'; 'Now I feel, *very sleepy–wide awake*': 'I fell asleep, *'never–immediately*'; and 'After I fell asleep I slept, *very badly–very well*'. In each case a favourable response tended toward the 100 extreme of the scale. The EEG and subjective data were analysed statistically. The coefficient of variability (s.d. × 100/mean) of each measure (C/V) was examined to decide whether an analysis of variance was appropriate. The arbitrary level was 50% and a non-parametric method (Friedmann two-way analysis of variance) was used for values exceeding 50%.

The residual effect of the drug (9 h after ingestion) was tested using digit symbol substitution. Examples from a series of 100 different sheets each with 200 randomized digits (0–9) arranged in 10 rows were presented (Nicholson & Stone, 1982). In the space under each digit the subjects were required to write the appropriate symbol indicated by a code at the top of each page. The code was different for each of the 100 sheets. In each session subjects were given two sheets and 2 min (timed separately) to complete as many substitutions as possible for each sheet. Errors were rare, and only the number attempted was analysed. Before the experiment began the subjects practised until they had reached steady performance, and this was confirmed in the analysis.

Results

The effects of brotizolam (0.25 mg), included as the active control, were similar to those observed previously in the same age group (Nicholson *et al.*, 1982). Total sleep time and the duration of stage 2 sleep were longer. Rapid eye movement (REM) sleep was reduced during the first 6 h, and a further analysis showed that this change was restricted to the first 2 h. There was no alteration in this measure when the analysis covered the whole night. Subjects considered their sleep improved and did not report a residual effect. There were no reductions in digit symbol substitution 9 h after ingestion.

The effects of midazolam (10, 20 and 30 mg) on sleep are given in Tables 1–6. The subjects as a group reported that they fell asleep faster and that their sleep was improved. There were no assessments of a residual effect (Table 7). The digit symbol substitu-

Table 1 Effect of midazolam on various sleep measures (means for six subjects)

Measures	*C/V*	*Placebo*	*Brotizolam (mg)*	*Midazolam (mg)*		
			0.25	*10*	*20*	*30*
Total sleep time (min)	3.8	438.2	459.0 *	450.3	468.5 **	461.5 *
Sleep-onset latency[a]	12.0	19.1	16.5	13.8	14.4 *	14.8
Latency (min) to stage REM	7.7	74.3	83.5	91.6	104.4	116.7
REM/NREM ratio	20.6	0.33	0.25	0.27	0.27 *	0.26
Sleep efficiency index[b,c]	14.5	0.90	0.93	0.92	0.95 *	0.94 *

C/V = coefficient of variability (s.d. × 100/mean) of each measure.
Significance levels: * $P < 0.05$; ** $P < 0.01$.
[a] Log (x) transform.
[b] Sleep efficiency index: total sleep time/time in bed.
[c] Log ($1 - x$) transform.

Table 2 Effect of midazolam on duration (min) of sleep stages over the whole night (means for six subjects)

Sleep stage	*C.V*	*Placebo*	*Brotizolam (mg)*	*Midazolam (mg)*		
			0.25	*10*	*20*	*30*
Awake	35.0	12.2	11.7	13.1	4.4	9.1
1	35.2	39.7	50.6	45.5	27.3	32.3
2	6.3	287.5	311.7	301.2	338.6	329.1
			*		***	***
3	75.4	6.2	7.3	12.5	5.5	6.8
3 + 4	76.0	6.2	7.3	12.6	5.5	6.8
REM	16.1	108.1	93.0	96.7	98.4	95.8

C.V = coefficient of variability (s.d. × 100/mean) for each measure.
Significance levels: * $P < 0.05$; *** $P < 0.001$.

Table 3 Effect of midazolam on percentage occupied by each sleep stage (means for six subjects)

Sleep stage	*C.V*	*Placebo*	*Brotizolam (mg)*	*Midazolam (mg)*		
			0.25	*10*	*20*	*30*
Awake	64.8	2.7	2.5	2.8	0.9	2.0
1	34.8	8.8	10.7	9.8	5.8	6.9
2	5.1	63.3	65.6	64.0	71.4	69.4
					***	**
3	74.7	1.4	1.6	2.7	1.2	1.5
3 + 4	75.3	1.4	1.6	2.7	1.2	1.5
REM	16.6	23.8	19.6	20.6	20.8	20.2

C.V = coefficient of variability (s.d. × 100/mean) for each measure.
Significance levels: ** $P < 0.01$; *** $P < 0.001$.

Table 4 Effect of midazolam on duration (min) of sleep stages in first 6 h of sleep (means for six subjects)

Sleep stage	*C.V*	*Placebo*	*Brotizolam (mg)*	*Midazolam (mg)*		
			0.25	*10*	*20*	*30*
Awake	47.5	8.2	5.8	4.9	2.9	2.6
1	33.6	27.5	26.0	23.3	17.2	16.6
					*	*
2	4.6	234.6	253.5	250.1	277.1	277.0
			**	*	***	***
3	75.4	6.2	7.3	12.5	5.5	6.8
3 + 4	76.0	6.2	7.3	12.6	5.5	6.8
REM	17.9	83.5	67.3	69.1	57.3	56.8
			*	*	**	**

C.V = coefficient of variability (s.d. × 100/mean) for each measure.
Significance levels: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

Table 5 Effect of midazolam on percentage occupied by each sleep stage in the first 6 h of sleep (means for six subjects)

Sleep stage	*C/V*	*Placebo*	*Brotizolam (mg)*	*Midazolam (mg)*		
			0.25	*10*	*20*	*30*
Awake	97.7	2.3	1.6	1.4	0.8	0.7
					*	
1	33.6	7.6	7.2	6.5	4.8	4.6
					*	*
2	4.6	65.2	70.4	69.5	77.0	76.9
			**	*	***	***
3 + 4	76.0	1.7	2.0	3.5	1.5	1.9
REM	17.9	23.2	18.7	19.2	15.9	15.8
			*	*	**	**

C/V = coefficient of variability (s.d. × 100/mean) of each measure.
Significance levels: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

Table 6 Effect of midazolam on 2-hourly distributions (min) of sleep stages (means for six subjects)

Sleep stage	*Interval*	*C/V*	*Placebo*	*Brotizolam (mg)*	*Midazolam (mg)*		
				0.25	*10*	*20*	*30*
Awake	0–2	98.8	1.6	2.7	0.8	1.3	0.5
	2–4	213.6	3.6	1.3	0.8	0.4	1.3
	4–6	95.3	3.0	1.8	3.4	1.2	0.8
							*
1	0–2	42.4	7.3	6.7	5.7	4.8	5.1
	2–4	43.9	8,2	9.8	7.3	5.3	5.4
	4–6	49.5	12.0	9.5	10.3	7.2	6.1
2	0–2	9.5	87.1	96.5	94.9	103.6	103.8
				*		**	**
	2–4	13.1	78.2	84.0	80.1	97.8	89.8
						**	*
	4–6	15.1	69.3	73.0	75.1	75.7	83.4
REM	0–2	61.2	18.5	7.1	10.3	5.0	3.7
				**	*	***	***
	2–4	38.0	29.4	24.6	27.6	16.3	23.5
	4–6	34.3	35.7	35.7	31.3	36.0	29.6

C/V = coefficient of variability (s.d. × 100/mean) for each measure.
Significance levels: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

Table 7 Effect of midazolam on subjective assessments of sleep and well-being (means for six subjects)

Assessment	*C/V*	*Placebo*	*Brotizolam (mg)*	*Midazolam (mg)*		
			0.25	*10*	*20*	*30*
A†	25.6	50.1	75.0	80.0	88.5	87.7
			**	***	***	***
B	22.1	72.9	74.5	72.0	61.2	62.5
C†	25.2	70.0	77.5	83.3	84.3	83.8
				*	*	*
D†	27.3	58.6	77.5	77.3	89.8	83.5
			**	*	***	***

C/V = coefficient of variability (s.d. × 100/mean) of each measure.
Assessment A: 'I slept, *very poorly–very well*'; B: 'Now I feel, *very sleepy–wide awake*'; C: 'I fell asleep, *never–immediately*'; D: 'After I fell asleep I slept, *very badly–very well*'.
Significance levels: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.
† Square root $(101 - x)$ transform.

Table 8 Effect of studied compounds on number of substitutions in digit symbol test (means for six subjects)

Placebo	*Brotizolam (mg)*	*Midazolam (mg)*		
	0.25	*10*	*20*	*30*
153.7	152.7	155.5	148.2	146.3

Error term DS: $F = 1.673$; $P = 0.18$. NS.

tion test did not show any residual decrements 9 h after ingestion of 10, 20 or 30 mg midazolam (Table 8).

Discussion

With 10 mg midazolam, sleep-onset latency was shorter, and the duration and percentage of stage 2 sleep were increased over the first 6 h. The duration and percentage of REM sleep were reduced; this was related to the first 2-hourly interval. There were no changes in total sleep time, and this, together with the alterations in sleep-onset latency, REM sleep, and the 2-hourly analyses, suggests that the activity of the 10 mg dose is limited to the early part of the night.

The effects of 20 and 30 mg midazolam were more pronounced than those of 10 mg, and were similar to each other. Sleep onset was earlier, total sleep times and stage 2 were increased, and the sleep efficiency indices were improved. During the first 6 h there was reduced duration and percentage of drowsy sleep. There was no evidence of delay to the first period of REM sleep, although the duration was reduced over the first 2 h. Essentially, 30 mg provided little additional improvement in sleep over the 20 mg dose, and this was also observed in the younger subjects (Nicholson & Stone, 1982).

We were unable to establish a residual effect even with 30 mg midazolam in the middle-aged group, and this was also our finding in young adults. We tested the possibility that a trend toward impaired performance was present over the dose range, but no such trend was established. These observations are consistent with the rapid elimination of the drug and would be compatible with the observation that duration of activity is unlikely to be extended significantly by increasing the dose (Amrein *et al.*, 1983).

In middle age, midazolam (10–30 mg) increased total sleep times and reduced sleep-onset latencies. This is of interest as with other benzodiazepines we have often been unable to establish such changes in the middle-aged, even though their total sleep times are shorter and their sleep-onset latencies are longer than young adults. However, other observations suggest that midazolam may be somewhat less effective in middle age. In the younger subjects there was an effect of even 10 mg midazolam on awake activity over the whole night, but this was seen only in the middle-aged group over the first 6 h. In young adults there was an increase in slow wave activity with both 20 and 30 mg, but no change in this measure was observed in the older group.

The picture from the present and previous studies is that midazolam is a useful short-acting hypnotic. However, in middle age, 10 mg may have a less overall effect, and 20 mg may be less active during the latter part of the sleep period. This may be related to the short duration of action of the drug in an age group in which sleep may be more disturbed during the latter part of the night. In young adults the initial, but limited, effect of midazolam may be followed by natural sleep. Clearly, 10–20 mg midazolam provides an adequate dose range free of adverse effects on sleep, and which is effective across the main span of life and free of residual effects the next day. The drug may be particularly useful in shiftworkers in whom rest periods tend to be shorter than in those who have a regular nocturnal sleep pattern.

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