MIDAZOLAM: EFFECTS ON PSYCHOMOTOR PERFORMANCE AND SUBJECTIVE ASPECTS OF SLEEP AND SEDATION IN NORMAL VOLUNTEERS

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- 1 Twelve healthy volunteers each received acute doses of placebo and 5, 10, 15 and 20 mg of midazolam. Seven subjects were tested before and 1, 4 and 7 h after treatment. Five subjects were given the same five treatments nocturnally and tested the following morning, 10–12 h after treatment.
- 2 Tests on various measures of sedation (choice reaction time and critical flicker fusion) and of drowsiness (line analogue rating scales) showed midazolam at 15 and 20 mg dose levels to be a potent sedative agent.
- 3 The present results suggest that the activity of midazolam is at a maximum 1 h after ingestion and that the effects of the drug have dissipated 7 h after treatment.

Introduction

The animal pharmacology of the water-soluble benzodiazepine midazolam and its human pharmacokinetics suggest the usefulness of the drug as a night-time hypnotic. The present study had two objectives. The first was to investigate the immediate effects of midazolam, over a range of doses, using both objective and subjective measures of drowsiness and sedative activity. The second was to observe the effects of an acute nocturnal dose of the drug on measures of psychomotor performance and mood the morning following treatment.

Methods

Subjects

Twelve healthy volunteers (eight female and four male) were used. None of the subjects was receiving any concurrent medication (apart from the contraceptive pill) and none had a history of cardiac, renal, gastrointestinal or mental disorder. Seven subjects (five female and two male) took part in the first experiment and five subjects (three female and two male) in the second. For the duration of the study subjects were not permitted to drive motor vehicles or to consume alcohol.

Assessments

Each subject received familiarization and training on each of the tests before experimentation began. For both parts of the study choice reaction time (CRT) performance and critical flicker fusion (CFF) levels were measured on the Leeds Psychomotor Tester (Hindmarch & Parrott, 1977; 1978). The mean response latency for sixty trials was the CRT measure taken and the CFF threshold was determined by the method of limits (Woodworth & Schlosberg, 1958) from six ascending and descending presentations of 4 light-emitting diodes in binocular vision at 1 metre.

Side-effects of treatment and subjective apperception of sedation were recorded on a set of 10-cm line visual analogue-rating scales (VARs; Gudgeon & Hickey, 1981). In the second part of the study subjective aspects of sleep and early morning behaviour were assessed on the Leeds Sleep Evaluation Questionnaire (LSEQ; Hindmarch, 1975; Parrott & Hindmarch, 1978, 1980).

Treatment regimen and procedure

Four doses of midazolam (5, 10, 15 and 20 mg), and a matching placebo were used. Each subject received all five treatment conditions in a randomized order.

Subjects acted as their own controls and treatments were given double-blind in accordance with a code broken only at the end of the study. A week-long 'washout period' was allowed between each treatment administration. In the first experiment seven subjects were assessed on the test measures immediately before and at 1, 4 and 7 h after administration of treatment. In the second part of the study the five subjects took their nocturnal treatment ½ h before retiring to bed and were tested the next morning, approximately 10 h later, between 09.00 and 09.30 a.m.

Statistical analysis

An analysis of variance was performed (a randomized block factorial design; Kirk, 1968) on the data. A planned comparison of treatment means was undertaken and two-tailed 97.5% confidence limits used to determine significant differences. Treatment means will be significantly different from each other, at a $P < 0.05$ or better, if the confidence limits for the two means do not overlap.

Results

Table 1 presents the mean results for the objective measures of sedation (CFF and CRT) together with 97.5% confidence limits (CL) for each dose level of midazolam. Table 2 presents the mean scores obtained on the subjective ratings of sedation from the VARS.

In both tables 0 mg of midazolam is to be regarded as matching placebo and 0 h is the pre-test baseline.

An analysis of variance was performed on the re-

sults of the overnight study; the means with standard errors of the means are given in Table 3.

To demonstrate the observed dose/response/time relationships the mean scores on total reaction time, critical flicker fusion thresholds and VARS ratings of drowsiness for each of the five treatments, at each of the four test times, are presented in Figures 1, 2 and 3.

Discussion

The results obtained for CRT show that as the dose of midazolam is increased there is a progressive and dose-related impairment of task performance, i.e. evidence of sedation. There is a significant interaction between the dose level of midazolam and the assessment session (time) factors. A consideration of the CRT results presented in Table 1 indicates the greatest impairment of CRT performance, all dose levels of midazolam taken into account, is at the 1 h post-administration assessment. After this 1 h post-treatment peak of impairment there is a progressive recovery, i.e. shortening of response latency, noticed on the CRT task, until at 7 h after medication the CRT latency approximates its pre-test baseline. The performance on this choice reaction time task is used here as an objective index of sedation. The sedative action of a drug, in reducing the level of activity of the central nervous system, reduces the level of integration between the sensory and motor systems and subjects take longer to effect the co-ordinated sensorimotor response required of them. Increasing the dose of midazolam is here associated with a lengthening of choice reaction time. This dose-related impairment of CRT performance with respect to time is illustrated in Figure 1 where it can be seen that, compared with all other doses, 20 mg of midazolam is especially sedative, 1 h after administration.

Table 1 The mean values (with standard errors of the mean) obtained on the two objective measures of sedation following the acute administration of midazolam

Test measure	Dose of midazolam (mg)	Time (h post-drug)				97.5% CL
		0	1	4	7	
CRT (ms) (n = 7)	0	445 (16.6)	458 (18.0)	471 (23.6)	450 (15.1)	126.3
	5	442 (18.5)	495 (17.5)	460 (11.4)	443 (11.0)	126.3
	10	448 (20.8)	681 (68.1)	467 (18.8)	457 (18.4)	126.3
	15	465 (19.4)	651 (94.7)	484 (13.0)	449 (14.2)	126.3
	20	482 (16.9)	1275 (245.3)	543 (48.9)	496 (24.4)	126.3
CFF (Hz) (n = 7)	0	30.7 (1.2)	30.4 (1.2)	29.8 (1.0)	31.4 (0.9)	0.9
	5	31.0 (1.6)	29.4 (1.3)	29.5 (1.0)	30.9 (1.1)	0.9
	10	31.3 (1.2)	28.1 (1.3)	30.3 (1.0)	30.9 (1.0)	0.9
	15	30.7 (1.4)	27.1 (1.4)	29.5 (1.1)	30.4 (1.7)	0.9
	20	30.1 (1.3)	26.7 (1.3)	28.8 (1.2)	30.0 (1.4)	0.9

Table 2 The mean values found on the visual analogue rating scales following treatment with a range of doses of midazolam ($n = 7$)

VARS (mm)	Dose of midazolam (mg)	Time (h post-drug)				97.5% CL
		0	1	4	7	
Tiredness	0	57	56	54	54	6.6
	5	56	58	58	57	6.6
	10	48	50	51	47	6.6
	15	58	61	57	55	6.6
	20	56	72	62	54	6.6
Drowsiness	0	53	53	52	48	5.9
	5	50	59	61	51	5.9
	10	51	61	53	51	5.9
	15	49	67	60	55	5.9
	20	47	72	63	53	5.9
Dizziness	0	50	48	51	50	4.7
	5	50	55	53	50	4.7
	10	50	62	53	50	4.7
	15	50	64	52	51	4.7
	20	50	66	59	51	4.7
Clumsiness	0	51	53	50	51	4.6
	5	50	57	52	52	4.6
	10	49	63	53	51	4.6
	15	50	66	53	51	4.6
	20	53	66	57	51	4.6
Alertness	0	50	50	50	54	6.2
	5	49	46	43	50	6.2
	10	47	42	48	48	6.2
	15	53	42	38	54	6.2
	20	49	34	45	47	6.2

Table 3 Means and (standard error of the means) for each of the overnight assessments ($n = 5$)

Assessment	Dose of midazolam					P
	0 mg (placebo)	5 mg	10 mg	15 mg	20 mg	
CRT (ms)	528 (16)	510 (17)	508 (21)	535 (27)	562 (19)	n.s.
CFF (Hz)	29 (1)	29 (0)	29 (0)	29 (1)	29 (0)	n.s.
VARS (mm)						
Tiredness	58 (6)	58 (5)	60 (1)	56 (4)	55 (3)	n.s.
Drowsiness	56 (6)	56 (5)	64 (2)	58 (4)	60 (6)	n.s.
Dizziness	51 (0)	51 (1)	56 (3)	50 (0)	54 (3)	n.s.
Clumsiness	56 (6)	55 (3)	67 (4)	56 (3)	61 (4)	n.s.
Alertness	45 (6)	44 (5)	38 (2)	47 (6)	35 (6)	n.s.
Energetic	48 (3)	44 (2)	41 (7)	47 (4)	38 (7)	n.s.
LSEQ (mm)						
Getting to sleep	48 (2)	60 (4)	63 (4)	61 (4)	60 (2)	n.s.
Quality of sleep	51 (3)	64 (5)	69 (5)	64 (7)	65 (4)	n.s.
Awakening	44 (4)	40 (6)	41 (7)	47 (3)	45 (2)	n.s.
Behaviour on waking	47 (3)	40 (4)	38 (1)	43 (2)	40 (5)	n.s.

Figure 1 Total reaction time for midazolam: 5 mg (□—□); 10 mg (○—○); 15 mg (■—■); 20 mg (●—●). Placebo (—).

CFF is a more direct measure of the level of central nervous system activity and sedative drugs have been shown (Hindmarch, 1980) to reduce the threshold. The results in Table 1, confirming the CRT findings, indicate that increasing the dose of midazolam increases its sedative activity. The CFF measures show maximum sedation at the 1 h post-drug assessment, after which there is a progressive recovery with the levels after 7 h equalling those obtained at the pre-test baselines. At 1 h, the CFF threshold after 5 mg of midazolam does not differ significantly from either placebo or its pre-test baseline. However, 10, 15 and 20 mg of midazolam produce a significant decrement

of CFF thresholds with respect to both their pre-test levels and the placebo control at 1 h.

The evident sedation shown on both CFF and CRT measures is reflected in the subjects' ratings of increased drowsiness, dizziness and tiredness along with concordant reductions in perceived alertness scored on the VARS (Table 2). The maximum subjective sedative effect is noted at 1 h when 20 mg midazolam produces significant changes, when compared with both pre-drug levels and placebo controls, on all VARS (Table 2, Figure 3).

Taking the CRT, CFF and VARS evidence together we can summarize that, compared with

Figure 2 Critical flicker fusion. Symbols as for Figure 1.

placebo, 10, 15 and 20 mg of midazolam all exhibit sedative activity 1 h after oral administration. However, it is only the two higher doses (15 and 20 mg) that show a significant and consistent sedative activity when compared with both pre-test baselines and placebo scores at 1 h. The results from both objective (CRT and CFF) and subjective (VARS) measures also show that all subjects have recovered from the sedation produced by midazolam when tested at 7 h post-drug.

In looking at the results from the second part of the study we must remember the preliminary nature of the investigation embodied in the use of only five subjects. However, the CRT and CFF measures in conjunction with VARS taken 10–12 h after the nocturnal ingestion of an acute dose of midazolam show no residual sedative activity to be present. These results augment the findings of our first experiment in showing that the sedation produced by midazolam (obvious 1 h after ingestion) is not detectable 10–12 h later.

There is a tendency for all dose levels of midazolam to improve the perceived ease of getting to sleep and the quality of sleep as measured on the LSEQ. More importantly, there is no evidence, from this subjective questionnaire, of any residual drug effects on early morning behaviour and performance. It was not the intention of this study to investigate the hypnotic activity of the drug and, in view of the small number of subjects taking part in this part of the experiment, it is not possible to draw any firm conclusions as to the effects of nocturnal doses of midazolam on sleep. However, it is possible to record the lack of any noticeable or significant drug-related sedation and impairment of behaviour the morning following acute doses of either 5, 10, 15 or 20 mg midazolam.

These present findings suggest that acute doses of midazolam 15 or 20 mg have a significant sedative effect an hour following ingestion. This sedation is not observed at 7 h or 12 h after drug administration.

Figure 3 Drowsiness as measured by visual analogue rating scales (in millimetres). Symbols as for Figure 1

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