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EFFECT OF MIDAZOLAM ON SLEEP OF INSOMNIACS

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1 We studied in a sleep laboratory the effects of bedtime 15 mg midazolam and 20 mg midazolam on the sleep and morning performance of healthy subjects with polygraphically verified sleep onset insomnia.

2 Six subjects received 15 mg midazolam and six subjects received 20 mg midazolam for 14 consecutive nights which were preceded by a three-night placebo baseline and followed by a three-night placebo period. The medications were administered in a double-blind manner.

3 The results were that both doses increased total sleep time, reduced sleep latency, reduced wake time after sleep onset and reduced the number of awakenings. There was no difference between the doses. Midazolam had its main effect by decreasing wake time in the first third of the night.

4 We found no evidence of tolerance, drug withdrawal rebound insomnia, or drug-induced morning performance decrements. We did find evidence of an anterograde amnesia produced by the drug.

Introduction

Midazolam is a new benzodiazepine with a plasma half-life of between 1.3 and 2.2 h and with sedative-hypnotic properties in animals (Pieri *et al.*, 1981). These characteristics suggest that in humans midazolam is an efficacious hypnotic with no morning hangover effect. We report a double-blind sleep laboratory test of this hypothesis. We studied the effect on sleep and morning performance of 15 and 20 mg midazolam in healthy adult patients with sleep onset insomnia.

Methods

Subjects

Subjects were 12 healthy adults with insomnia as defined below. Three males and nine females with a mean age of 51 years (range 39–63 years) were studied. All subjects had both subjective and objective insomnia. Subjective insomnia was a minimum 6-month history of requiring at least 60 min to fall asleep on at least 50% of nights. Objective insomnia was determined polysomnographically within 3 months of study entry. Objective insomnia was a median sleep latency of 30 min or longer during nights 2–4 of 4 consecutive sleep-laboratory nights. All subjects were physically healthy as determined by an internist's pre-study history and physical examination and by clinical laboratory tests (SMA-12, CBC, EKG, and urinalysis). In particular, we excluded any person with mental retardation, significant psychiatric illness, history of drug abuse, or any condition that might interfere with the sleep cycle or with the disposition of a benzodiazepine. By history all subjects had taken no drugs for 10 days before study entry and had taken no long-acting hypnotics or sedatives for 30 days before study entry.

Procedure

Six randomly selected subjects were treated with 15 mg midazolam and the remaining six subjects were treated with 20 mg midazolam on the following 12-night schedule: night 1, placebo (laboratory adaptation); nights 2–4, placebo (baseline); nights 5–18, 15 or 20 mg; nights 19–21, placebo (drug withdrawal). Except for nights 12–14 (i.e. drug nights 8–10) which were spent at home, all nights were spent in the sleep laboratory with polysomnographic recordings. These consisted of continuous all-night, conventional EEG, EOC, EMG recordings. Neither subjects nor laboratory technicians were aware of the study design.

During each subject's sleep-laboratory nights, total

recording time (i.e. bedtime plus any time up to use the toilet) was 480 min. Medication was administered exactly 30 min before lights-out (bedtime).

Sleep parameters

Using the standard Rechtschaffen-Kales Manual (Rechtschaffen & Kales, 1968), we determined the following polysomnographic variables: total sleep time, sleep percentage of total recording time, stage 1 sleep latency (time from lights-out to first half minute of stage 1 sleep); stage 2 sleep latency (time from lights-out to first half minute of stage 2 sleep); wake time in each third of the recorded night; total wake time; wake time after onset of stage 1; number of awakenings of at least 15 s duration; stages 1, 2, delta and REM in minutes and percentage of total sleep time; stage REM time in each third of the night; REM latency (duration of NONREM sleep preceding first half minute of stage REM); movement time; and total recording time.

Subjective estimates of sleep were obtained by morning completion of the Bond scale. On this scale subjects estimated their quality of sleep, onset of sleep, feeling on awakening, and feeling 30 min after awakening.

Safety

Safety was assessed: (1) by pre- and post-study physical examinations and clinical laboratory tests (CBC, urinalysis, SMA-12, and EKG); (2) by screening physicals (standing and supine blood pressure and pulse, and oral temperature) done each laboratory morning and evening; (3) by completion of an 11-item hypnotic drug side-effect questionnaire each laboratory morning and evening; (4) by the following psychomotor performance tests, done each laboratory morning (Purdue peg board tasks, platform balance skill, and digit symbol substitution test).

These tests may be described in the following manner. In the digit symbol substitution test each of the numbers 1–9 is matched with a different geometric symbol. With the digit symbol correspondence in view, the subject is presented with 390 randomly ordered digits, each digit with a space under it. In each of these spaces the subject is asked to write, as quickly as possible, the symbol corresponding to the above digit. The score is the number of correctly matched symbols written in 5 min.

In the platform balance test the subject stands on a 13 inch square board positioned on a 2 inch high fulcrum. The subject attempts to balance the board on the fulcrum for as long as possible and to bring the board into balance for as many times as possible in a 1 min trial. The score is the mean time off balance and the mean number of times off balance in four 1 min trials.

The Purdue peg board tasks are done on an 11¼ × 17½ inch board with two columns of 25 holes each. The holes are ⅛ inch in diameter. The columns of holes are 1 inch apart and the rows of holes are a ½ inch apart. The equipment includes pegs that fit the holes, and washers and cylindrical collars that fit onto the pegs. In the preferred hand task, the subject is instructed to use the preferred hand to place as many pegs as possible into holes in 1 min. In the non-preferred hand task and in the both hands task, the subject receives the same instructions for the non-preferred and for both hands, respectively. The score, in each of the tasks, is the number of pegs inserted into holes in 1 min. In the non-preferred hand task and in the both hands task, the subject receives the same instructions for the non-preferred and for both hands, respectively. The score, in each of the tasks, is the number of pegs inserted into holes in 1 min. In the assembly task, the subject is instructed to construct the following assembly as many times as possible in 1 min: peg in hole with the preferred hand, the washer over the inserted peg with the non-preferred hand, then cylindrical collar on top of the washer with the preferred hand, and finally a washer on top of the collar with the non-preferred hand, then repeat assembly as many times as possible. The score is the number of parts correctly assembled in 1 min.

Results

Polysomnographic efficacy variables (Table 1)

As measured by baseline-drug period differences, both the 15 and 20 mg doses of midazolam significantly increased total sleep time, and significantly decreased wake time in the first third of the night.

The increase of sleep time was usually about 35–40 min at each dose. The decrease of wake time in the first third of the night was usually to about 50% of baseline values. These results occurred on the first drug night, on the mean of drug nights 1–7, on the mean of drug nights 11–14, and on the last (14th) drug night. The two doses of midazolam had various effects on wake time in the second third of the night, sometimes reducing it and other times not doing so. Neither dose of midazolam significantly reduced wake time in the last third of the night. There was no significant difference between the two doses in their effects on total sleep time and on wake time in each third of the night.

Both doses of midazolam reduced stage 1 sleep latency and stage 2 sleep latency. The effect of 15 mg midazolam was significant at $0.05 < P < 0.10$ and the effect of 20 mg midazolam was significant at $P < 0.05$. Again these effects were significant throughout the 14 nights of drug administration and there was no signifi-

Table 1 Polysomnographic efficacy variables

	Midazolam (15 mg)						*Midazolam (20 mg)*					
	BSL	*D1*	*D1–7*	*D11–14*	*D14*	*PD1*	$\overline{PD}$	*BSL*	*D1*	*D1–7*	*D11–14*	*D14*	*PD1*	$\overline{PD}$
TST	390	438*	426**	429*	431**	367	382	398	433**	436**	432**	442**	396	400
SL-1	30	17†	18†	15	12†	82	56	39	21**	20**	23**	17*	46	37
SL-2	37	23†	22†	18†	16†	86	61	42	23**	22**	24**	18*	53	42
WT(1/3)	47	21**	22**	18*	14**	67	55	55	25**	24**	26**	20**	60	47
WT(2/3)	14	8	4*	4*	3*	30	16	10	4†	4*	5	4	7	7
WT(3/3)	23	7†	22	23	26	13	24	13	12	11	14	12	14	23
Post-S-1 WT	53	18**	31†	30*	31	28†	38	40	19*	19*	23†	19*	35	40
Wakes (*n*)	12	7†	9†	13	14	11	14	16	8*	9*	13	14	17	16

BSL, baseline; D1, first drug night; D1–7, first to seventh drug nights; D11–14, eleventh to fourteenth drug nights; D14, fourteenth drug night; PD1, first post-drug night; $\overline{PD}$, mean post-drug night; TST, total sleep time; SL-1, SL-2, sleep latencies to stage 1 and stage 2, respectively; WT(1/3), WT(2/3), WT(3/3), wake time in first, second, and third thirds of the recorded night, respectively; Post-S-1 WT, wake time after onset of stage 1. Entries are in minutes.

Matched pair *t*-tests, one tailed for baseline-drug night differences and two tailed for baseline post-drug night differences:

* $P < 0.05$

** $P < 0.01$

† $P < 0.1$

cant difference between the two doses in their effects on sleep latencies.

Both doses of midazolam significantly reduced total wake time after the onset of stage 1; this indicates that the drug had a sleep maintenance effect as well as an effect in reducing sleep latency. The effect on wake time after sleep onset was present throughout the period of drug administration at both doses with the following exception: 15 mg of midazolam did not reduce wake time after sleep onset on the last (14th) drug night.

Both doses of midazolam reduced the number of awakenings during the first 7 drug nights and during nights 11–14. Again at 15 mg the effect was significant at $P < 0.10$ and at 20 mg the effect was significant at $P < 0.05$. Again, there was no significant difference between the doses in their effect on number of awakenings.

Neither dose had a significant effect on early morning awakening.

To test for development of tolerance to the hypnotic effects of the drug, we assessed first drug night versus the 14th drug night differences in each variable. We found no significant differences at each dose and thus no evidence of tolerance.

To test for rebound insomnia, we assessed baseline versus first post-drug night differences in each variable and baseline versus mean post-drug night differences in each variable. We found no significant differences at each dose and thus no evidence of rebound insomnia.

Safety

There were no clinically significant differences in pre- and post-study physical examinations and pre- and post-study clinical laboratory tests (CBC, urinalysis, SMA-12, and EKG).

At each dose, baseline-drug period differences in the measures of adverse effects were not significant. These measures included the morning and evening 11-item hypnotic drug side-effect questionnaires, the psychomotor performance tests, (digit symbol substitution test, Purdue peg board assembly, and platform balance task), and vital signs. There were two exceptions to this rule. Firstly, in the platform balance task there was an improvement on the first night of the 20 mg dose, and, secondly, in the Purdue peg board assembly, there was improved performance during the last three drug nights at each dose. These improvements were part of a trend over the whole experiment and almost certainly represented a learning curve. Tables 2–7 present the analysis of results obtained for each of the tests of psychomotor performance.

However, three subjects (two on 15 mg and one on 20 mg midazolam) reported distressing anterograde amnesia for 0.25–1 or more hours after drug adminis-

Table 2 Platform balance (seconds offbalance)

	BSL	*D1*	*D1–7*	*D11–14*	*D14*	*PD1*	*PD1–3*
Mean (15 mg)	41.2	39.5	39.9	40.5	40.0	39.2	39.3
BSL *v.* all post-BSL		n.s.	*	n.s.	n.s.	n.s.	n.s.
D1 *v.* D11–14, D14				n.s.	n.s.		
D1–7 *v.* D11–14				n.s.			
Mean (20 mg)	39.7	37.8	38.0	37.7	37.7	38.1	37.3
BSL *v* all post-BSL		*	n.s.	n.s.	n.s.	n.s.	n.s.
D1 *v.* D11–14, D14				n.s.	n.s.		
D1–7 *v.* D11–14				n.s.			

Except for single night entries, all entries are means of the indicated period. BSL, baseline; D1, first drug night; D1–7, drug nights one to seven; D11–14, drug nights eleven to fourteen; D14, fourteenth (last) drug night; PD1, first post-drug night; PD1–3, first to third post-drug nights.
Matched pair *t*-tests, two tail:
$*P < 0.05$
$**P < 0.01$
n.s., not significant.

Table 3 Purdue peg board: preferred hand task (number of pegs inserted)

	BSL	*D1*	*D1–7*	*D11–14*	*D14*	*PD1*	*PD1–3*
Mean (15 mg)	14.9	14.9	14.9	15.3	15.5	15.2	15.7
BSL *v.* all post-BSL		n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
D1 *v.* D11–14, D14				n.s.	n.s.		
D1–7 *v.* D11–14				n.s.			
Mean (20 mg)	16.9	15.8	16.8	17.3	17.4	17.7	17.5
BSL *v.* all post-BSL		n.s.	n.s.	n.s.	*	n.s.	n.s.
D1 *v.* D11–14, D14				n.s.	n.s.		
D1–7 *v.* D11–14				n.s.			

Except for single night entries, all entries are means of the indicated period.
Symbols and abbreviations: see Table 2.

Table 4 Purdue peg board: non-preferred hand task (number of pegs inserted)

	BSL	*D1*	*D1–7*	*D11–14*	*D14*	*PD1*	*PD1–3*
Mean (15 mg)	13.9	14.7	14.6	14.6	15.1	14.6	15.0
BSL *v.* all post-BSL		n.s.	n.s.	*	*	n.s.	*
D1 *v.* D11–14, D14				n.s.	n.s.		
D1–7 *v.* D11–14				n.s.			
Mean (20 mg)	15.1	14.2	15.2	15.6	15.8	15.9	16.1
BSL *v.* all post-BSL		n.s.	n.s.	n.s.	n.s.	n.s.	*
D1 *v.* D11–14, D14				n.s.			
D1–7 *v.* D11–14				n.s.			

Except for single night entries, all entries are means of the indicated period.
Symbols and abbreviations: see Table 2.

Table 5 Purdue peg board: both hands task (number of pegs inserted)

	BSL	*D1*	*D1–7*	*D11–14*	*D14*	*PD1*	*PD1–3*
Mean (15 mg)	20.9	22.0	23.0	24.7	24.0	23.0	24.0
BSL *v.* all post-BSL		n.s.	n.s.	n.s.	n.s.	*	*
D1 *v.* D11–14, D14				*	*		
D1–7 *v.* D11–14				n.s.			
Mean (20 mg)	21.2	23.8	24.6	26.2	25.8	24.8	25.8
BSL *v.* all post-BSL		n.s.	n.s.	*	**	n.s.	*
D1 *v.* D11–14, D14				n.s.	n.s.		
D1–7 *v.* D11–14				n.s.			

Except for single night entries, all entries are means of the indicated period.
Symbols and abbreviations: see Table 2.

Table 6 Purdue peg board: number of parts assembled

	BSL	*D1*	*D1–7*	*D11–14*	*D14*	*PD1*	*PD1–3*
Mean (15 mg)	27.6	31.8	33.9	35.4	35.2	35.8	37.6
BSL *v.* all post-BSL		n.s.	*	*	*	*	*
D1 *v.* D11–14, D14				*	n.s.		
D1–7 *v.* D11–14				*			
Mean (20 mg)	21.2	23.8	24.6	26.2	25.8	24.8	25.8
BSL *v.* all post-BSL		n.s.	n.s.	**	**	n.s.	*
D1 *v.* D11–14, D14				n.s.	n.s.		
D1–7 *v.* D11–14				n.s.			

Except for single night entries, all entries are means of the indicated period.
Symbols and abbreviations: see Table 2.

Table 7 Digit symbol substitution test (% correct)

	BSL	*D1*	*D1–7*	*D11–14*	*D14*	*PD1*	*PD1–3*
Mean (15 mg)	99.5	99.5	99.4	99.8	99.8	99.8	99.4
BSL *v.* all post-BSL		n.s.	n.s.	n.s.	n.s.	*	n.s.
D1 *v.* D11–14, D14				n.s.	n.s.		
D1–7 *v.* D11–14				n.s.			
Mean (20 mg)	99.2	99.0	99.0	99.3	99.3	99.8	99.6
BSL *v.* all post-BSL		n.s.	n.s.	n.s.	n.s.	*	n.s.
D1 *v.* D11–14, D14				n.s.	n.s.		
D1–7 *v.* D11–14				n.s.			

Except for single night entries, all entries are means of the indicated period.
Symbols and abbreviations: see Table 2.

tration. One of these subjects (who received 20 mg of midazolam) reported anterograde amnesia on her third and fourth drug nights and left the study after her fourth drug night. A second subject, who received 15 mg of midazolam, reported anterograde amnesia on her sixth drug night and possibly earlier. She also dropped out. A third subject, who received 15 mg of midazolam, reported anterograde amnesia and daytime problems in concentration during her second drug week. She did not drop out. All subjects had no further symptoms and normal mental status examinations the day after their nocturnal complaints.

Sleep stages

Neither dose of midazolam had a significant effect on delta sleep. The effects of the drug on REM sleep were small. The 15 mg, but not the 20 mg, dose decreased REM sleep for the first third of the night. Neither dose affected REM sleep in the second or last third of the night or affected total nocturnal REM sleep. Both doses prolonged REM latency on some but not on all drug nights. There was no evidence of significant REM rebound on the first post-drug night or the mean post-drug night. However, in the 15 mg group, but not in the 20 mg group, REM time in the first third of the night was significantly reduced on the first and mean post-drug night.

Discussion

Midazolam, in doses of 15 and 20 mg is an efficacious hypnotic. As assessed by the polysomnograph, both doses increased total sleep time, reduced sleep latency and decreased the number of nocturnal awakenings. Midazolam appeared to have its maximum effect in the early part of the night.

As assessed by subjective ratings, both doses reduced sleep latency and improved the quality of sleep. Although the effects of 20 mg were descriptively stronger than the effects of 15 mg, there was no significant difference between the two doses in their effects on efficacy variables.

We found no evidence of the development of tolerance to the 14 consecutive nights of drug administration. We found no consistent evidence of rebound insomnia on discontinuation of the drug. This is remarkable in view of the hypothesis that short-acting benzodiazepines such as midazolam may produce a rebound insomnia (Kales *et al.*, 1978).

We found no evidence that either dose impaired performance the morning after drug administration or produced adverse effects on the physical examination, EKG, urine or blood test. Since benzodiazepines with a long half-life do produce daytime performance decrements (Oswald *et al.*, 1979), midazolam with its short half-life would seem to have some advantage. The improvements in performance, however, were part of a trend over the whole experiment and almost certainly represented a learning effect.

Three of 14 subjects developed anterograde amnesia for a few hours after drug administration. This is not an unusual effect of benzodiazepine hypnotics (Roth *et al.*, 1980).

These findings suggest that midazolam is an efficacious hypnotic particularly for the treatment of sleep onset insomnia and that the 15 mg dose may be as effective as the 20 mg dose. By comparison with other benzodiazepine hypnotics (Vogel *et al.*, 1976) our findings suggest that midazolam may be as efficacious as longer-acting agents, and possibly without producing either rebound insomnia or daytime performance decrements.

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