EFFECT OF MIDAZOLAM ON SLEEP

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1 Midazolam (15 mg p.o.) was compared with placebo and oxazepam (15 mg) in 12 healthy volunteers and in seven patients suffering from sleep disorders in a single-blind cross-over study. Each treatment period lasted for seven days. The last two nights were spent in a sleep laboratory to evaluate the efficacy of the three compounds. The drugs were given to the patients every day and to the volunteers only on the recorded nights immediately before going to bed. The subjects rated their quality of sleep every morning after administration.

2 Midazolam shortened ($P = 0.025$) the sleep latency to first stage 2 ($t_2 = 29$ min) compared with placebo ($t_2 = 58.7$) min and oxazepam ($t_2 = 55.4$ min) in the group of patients; in the group of volunteers t_2 was shortened ($P = 0.05$) only by midazolam ($t_2 = 17.2$ min) compared with placebo ($t_2 = 24.6$ min). REM suppression was not found in the group of patients, while sleep stages 3 + 4 were slightly reduced. However, a suppression of REM by midazolam ($P = 0.025$) and oxazepam ($P = 0.01$) was observed in the volunteers compared with placebo.

3 The effects of midazolam seemed to be related to its pharmacokinetics. The drug increased the amount of stage 3 + 4 ($P = 0.01$) and suppressed REM ($P = 0.005$) compared with oxazepam and placebo, only during the first 3 h, when it was measurable in plasma. Midazolam was rated by the patients more favourably than oxazepam ($P = 0.025$) and placebo ($P = 0.05$).

4 The volunteers noted no difference amongst the three treatments, but reported hangover effects after oxazepam.

Introduction

Midazolam is a new short-acting and water-soluble 1,4-benzodiazepine, which has been used in man for intravenous induction of anaesthesia (Conner *et al.*, 1978). Our kinetic data (Allonen *et al.*, 1981) evaluated after single oral (15 mg) or intravenous (0.075 mg kg⁻¹) doses and steady-state infusion programs have demonstrated a rapid blood-flow-dependent (blood clearance of about 500 ml min⁻¹) hepatic elimination which is subject to alterations according to the time of the day and body position (Klotz & Ziegler, 1982). Since its absorption is also rapid (mean $t_{1/2} = 0.23$ h), midazolam might be an alternative in the treatment of insomniacs especially in those with difficulties in falling asleep. The present study reports some sleep-laboratory data on the efficacy of midazolam, compared with placebo and oxazepam in seven severely sleep-disturbed patients and in 12 healthy volunteers.

Methods

Subject selection

Seven patients (four female and three male, mean age 53.1 ± 4 years) with severe and long-lasting (as a mean for 13.8 years) functional sleep disorders were selected for the clinical study. The prior medication in the patients was oxazepam (three cases), bromazepam (two cases), lorazepam (one case), diphenhydramine (one case) and barbiturate (one case). The group of 12 male healthy volunteers (mean age 21 ± 1.7 years) had no sleep difficulties and were free of any drugs. All subjects were screened to eliminate those with a history of medical disorders, psychoses, drug or alcohol abuse, and those currently using other medications.

Design of study

The study was carried out in a single-blind cross-over

design consisting of three periods. Each period lasted 7 days and the last 2 days were spent in the sleep laboratory. Patients were given daily in the first week 15 mg of oxazepam (similar to their prior medication), in the second week identical placebo (wash-out phase), and in the last week identical 15 mg midazolam tablets. Healthy volunteers received the drugs according to the above protocol only on the two consecutive nights recorded. The tablets were always given immediately before going to bed.

Throughout the study the subjects were instructed not to use any other medications. All subjects were informed about the nature of the experiment and their written consent was obtained.

During each night (always the same two consecutive days of the week) the subjects' sleep EEG (one EEG, one EMG and two EOG recordings) were continuously monitored by a Beckman eight-channel polygraph (R 612). All sleep records were scored according to standardized criteria (Rechtschaffen & Kales, 1968) by a trained rater. Throughout the study, subjects completed a questionnaire each morning (a nine-point subjective rating scale) on sleep quality and were asked about hangover effects.

The dependent variables assessed were:

- 1 The subjective rating of the sleep quality as the mean over the whole period (patients) or the two laboratory nights (volunteers), respectively.
- 2 The sleep EEG: sleep latency (to first stage 2), amount of slow-wave sleep (stage 3 + 4), amount of REM sleep, amount of wake time after sleep onset, frequency of sleep-stage changes, shifts to stage 1, awake and moving time, latencies to stage 3, 4, REM, total wake time, total stage 1 and stage 2 sleep.
- 3 The distribution of slow-wave sleep and REM sleep over the night in intervals of the first 3 h and the rest of the night.

Statistical analysis

The data of the three treatments were compared by the paired Student's *t*-test and by the Wilcoxon test. Individual mean values of the two sleep-laboratory nights from each period were used to evaluate the effect of the compounds. All values given represent mean $\pm$ standard deviation ($\bar{x} \pm$ s.d.).

Results

Insomniacs

The mean results (see Table 1) of the sleep patterns show that midazolam significantly shortened ($P = 0.025$) the sleep latency to the first stage 2 sleep (29 min) compared with placebo and oxazepam. There was no difference between oxazepam (55 min) and placebo (59 min). The amount of slow-wave sleep

(stage 3 + 4) was not different between placebo and oxazepam, but was slightly reduced ($P < 0.1$ Wilcoxon or $P = 0.05$ *t*-test) by midazolam. The values obtained (between 21 and 32 min) are typical for sleep-disturbed patients. The amount of REM sleep and the latency to REM were nearly identical under the three conditions; a REM suppression in the insomniacs could not be found with the two benzodiazepines. There was a trend toward a decrease in the amount of intervening wakefulness and total wake time by midazolam. The frequency of changes between several sleep stages and shifts to stage 1, wake and moving time (comparable with the number of awakenings) was slightly reduced by midazolam.

The distribution of REM sleep and slow-wave sleep within intervals of 3 h showed no significant differences. The subjective rating of the sleep quality demonstrated an improvement under midazolam compared with placebo ($P = 0.05$) and with oxazepam ($P = 0.025$ *t*-test or $P = 0.1$ Wilcoxon).

Healthy volunteers

The results (see Table 2) indicate that the mean sleep latency to first stage 2 is reduced significantly under midazolam only if compared with placebo ($P = 0.05$). The amount of slow-wave sleep was similar under all three conditions while the REM sleep was suppressed under both benzodiazepines ($P = 0.01$). The slight difference between midazolam (76 min) and oxazepam (84 min) was not significant. A significant, but clinically not relevant (see values in Table 2), reduction in the amount of intervening wakefulness ($P = 0.01$) and in the amount of the total wake time ($P = 0.005$) was found with midazolam compared with placebo and oxazepam. A reduction ($P = 0.05$) under both benzodiazepines was found for the frequency of sleep-stage changes, but only midazolam reduced the frequency of shifts to stage 1, wake and moving time (comparable with the number of awakenings) compared with oxazepam ($P = 0.05$) and placebo ($P = 0.005$).

From our own pharmacodynamic and pharmacokinetic studies (Allonen *et al.*, 1981; Klotz & Ziegler, 1982) we know that midazolam is measurable in effective plasma concentrations only for the first 3 h. During this period (see Table 3) in our study, it significantly suppressed the amount of REM sleep compared with placebo and oxazepam ($P = 0.005$); consequently the significant ($P < 0.01$) prolongation of the REM latency, was highest under midazolam (see Table 2). Oxazepam also reduced the REM sleep ($P = 0.005$), but this effect lasted over the whole night. The amount of REM sleep in the rest of the night was similar between placebo and midazolam (79.8 and 72.3 min, respectively).

The distribution (see Table 3) of the effects of the first 3-h interval (based on the pharmacokinetics of

Table 1 EEG data and sleep quality (mean $\pm$ s.d.) in the group of insomniacs ($n = 7$)

	<i>Oxazepam</i>	<i>Placebo</i>	<i>Midazolam</i>
Total sleep time (% of bed time)	74.4 $\pm$ 12.4	74.0 $\pm$ 10.2	81.3 $\pm$ 12.3
	n.s.		n.s.
Total wake-time (min)	116.8 $\pm$ 57.4	125.5 $\pm$ 52.3	87.5 $\pm$ 56.8
	n.s.		n.s.
Sleep latency (min) (to first stage 2)	55.4 $\pm$ 31.9	58.7 $\pm$ 43.6	29.0 $\pm$ 12.8
	n.s.		$P = 0.025$
Latency to stage 3 (min)	105.6 $\pm$ 143.0	42.9 $\pm$ 28.0	183.2 $\pm$ 178.5
	n.s.		$P = 0.005$
Latency to stage 4 (min)	191.0 $\pm$ 120.3	214.8 $\pm$ 148.7	255.6 $\pm$ 174.7
	n.s.		n.s.
Slow-wave sleep (min) (stage 3 + 4)	29.2 $\pm$ 28.5	32.3 $\pm$ 24.7	20.9 $\pm$ 19.7
	n.s.		n.s.
REM latency (min)	159.5 $\pm$ 52.6	124.4 $\pm$ 46.6	154.9 $\pm$ 80.6
	n.s.		n.s.
REM sleep (min)	55.1 $\pm$ 25.7	68.3 $\pm$ 12.1	68.5 $\pm$ 38.9
	n.s.		n.s.
Total stage 1 sleep (min)	39.9 $\pm$ 24.6	36.1 $\pm$ 12.6	22.4 $\pm$ 7.8
	n.s.		$P = 0.025$
Total stage 2 sleep (min)	225.8 $\pm$ 36.4	220.6 $\pm$ 44.1	277.3 $\pm$ 42.2
	n.s.		$P = 0.025$
	$P = 0.05$		
Wake time after sleep onset (min)	75.2 $\pm$ 37.4	80.9 $\pm$ 32.4	63.3 $\pm$ 51.4
	n.s.		n.s.
Changes between sleep stages (frequency)	86.1 $\pm$ 31.2	90.6 $\pm$ 23.0	69.4 $\pm$ 25.5
	n.s.		n.s.
Shifts to wake, stage 1 and moving time (frequency)	23.2 $\pm$ 9.5	26.9 $\pm$ 10.4	20.4 $\pm$ 9.1
	n.s.		n.s.
Sleep quality (1 = very poor 9 = excellent)	4.9 $\pm$ 1.9	5.4 $\pm$ 1.7	6.7 $\pm$ 0.7
	n.s.		$P = 0.05$

For comparison the Wilcoxon test for paired data was used.

Table 2 EEG data and sleep quality (mean $\pm$ s.d.) in the group of healthy volunteers ($n = 12$)

	<i>Oxazepam</i>	<i>Placebo</i>	<i>Midazolam</i>
Total sleep time (% of bed time)	92.5 $\pm$ 3.1	95.0 $\pm$ 2.5	97.9 $\pm$ 1.3
	$P = 0.05$		$P = 0.01$
	$P = 0.01$		
Total wake time (min)	33.5 $\pm$ 17.1	21.5 $\pm$ 11.7	9.1 $\pm$ 5.6
	$P = 0.025$		$P = 0.005$
	$P = 0.005$		
Sleep latency (min) (to first stage 2)	26.9 $\pm$ 20.0	24.6 $\pm$ 15.3	17.2 $\pm$ 6.5
	n.s.		$P = 0.05$
	n.s.		
Latency to stage 3 (min)	20.3 $\pm$ 9.3	19.0 $\pm$ 5.4	16.1 $\pm$ 5.1
	n.s.		n.s.
	n.s.		
Latency to stage 4 (min)	58.3 $\pm$ 73.4	51.8 $\pm$ 68.2	53.0 $\pm$ 68.1
	n.s.		n.s.
	n.s.		
REM latency (min)	149.3 $\pm$ 18.1	127.5 $\pm$ 19.0	209.5 $\pm$ 44.8
	$P = 0.01$		$P = 0.0005$
	$P = 0.005$		
Slow-wave sleep (min) (stage 3 + 4)	86.9 $\pm$ 19.9	93.8 $\pm$ 34.7	95.8 $\pm$ 21.9
	n.s.		n.s.
	n.s.		
REM sleep (min)	84.8 $\pm$ 32.2	102.8 $\pm$ 26.6	76.0 $\pm$ 16.7
	$P = 0.01$		$P = 0.025$
	n.s.		
Total stage 1 sleep (min)	15.4 $\pm$ 9.3	16.5 $\pm$ 9.8	7.8 $\pm$ 4.5
	n.s.		$P = 0.005$
	$P = 0.025$		
Total stage 2 sleep (min)	229.2 $\pm$ 36.1	194.6 $\pm$ 30.1	223.0 $\pm$ 27.2
	$P = 0.05$		$P = 0.025$
	n.s.		
Wake time after sleep onset (min)	7.6 $\pm$ 7.8	4.6 $\pm$ 4.7	1.1 $\pm$ 3.4
	n.s.		$P = 0.01$
	$P = 0.01$		
Changes between sleep stages (frequency)	45.9 $\pm$ 21.6	50.6 $\pm$ 20.9	40.7 $\pm$ 13.8
	$P = 0.05$		$P = 0.01$
	n.s.		
Shifts to wake, stage 1, and moving time (frequency)	10.0 $\pm$ 4.4	11.7 $\pm$ 3.1	7.5 $\pm$ 1.9
	n.s.		$P = 0.005$
	$P = 0.05$		
Sleep quality (1 = very poor 9 = excellent)	6.2 $\pm$ 1.2	5.8 $\pm$ 1.7	6.2 $\pm$ 1.0
	n.s.		n.s.
	n.s.		

All comparisons are using the Wilcoxon test for paired data.

Table 3 Amounts of slow-wave sleep and REM sleep (mean $\pm$ s.d.) divided into two parts according to the pharmacokinetics of midazolam in healthy volunteers ($n = 12$)

	Oxazepam	Placebo	Midazolam
Stage 3 + 4 (min)	56.2 $\pm$ 22	57.9 $\pm$ 18	76.4 $\pm$ 15
0-3 h	<div style="display: flex; justify-content: space-around; align-items: center;"> _____ n.s. _____ _____ P = 0.005 _____ </div>		
3 h-end	30.8 $\pm$ 21.2	34.8 $\pm$ 27.2	19.6 $\pm$ 18.3
	<div style="display: flex; justify-content: space-around; align-items: center;"> _____ n.s. _____ _____ P = 0.005 _____ </div>		
REM sleep (min)	15.6 $\pm$ 15	24.2 $\pm$ 15	3.8 $\pm$ 3.5
0-3 h	<div style="display: flex; justify-content: space-around; align-items: center;"> _____ P = 0.005 _____ _____ P = 0.005 _____ </div>		
3 h-end	69.5 $\pm$ 21.5	79.8 $\pm$ 21.6	72.3 $\pm$ 14.9
	<div style="display: flex; justify-content: space-around; align-items: center;"> _____ P = 0.025 _____ _____ n.s. _____ </div>		

All comparisons are using the Wilcoxon test for paired data.

midazolam) and the rest of the night indicate that midazolam increases the amount of slow-wave sleep in the first 3 h compared with placebo and oxazepam ($P = 0.005$ and $P = 0.01$, respectively). In contrast, we found a decrease of slow-wave sleep under midazolam compared with placebo in the rest of the night ($P = 0.005$) and a large variation in the difference with oxazepam. The subjective rating of sleep quality showed no difference, but the volunteers reported more hangover effects after oxazepam (nine cases) than following placebo (two cases) and midazolam (two cases).

Discussion

Dependent on the group of subjects studied, we found different results of the two benzodiazepines studied. In addition both drugs demonstrated some qualitative differences in the objective sleep pattern and subjective ratings. An effect in terms of reducing sleep latency was visible in both groups with midazolam. This has important clinical implications especially in the group of insomniacs. Surprisingly this effect was also seen in the healthy volunteers who already have a short t_2 time. Most likely this is due to the very rapid absorption of midazolam (Allonen *et al.*, 1981). The absorption of oxazepam is slow, so we could not expect a reduction in sleep latency by taking the tablet at the same time.

Both benzodiazepines cause a marked REM suppression and prolongation of REM latency in healthy volunteers, while these effects were not visible in insomniacs. We suggest that the small amount of REM already present in the insomniacs, which is comparable to literature data of about 76-98 min (Frankel *et al.*, 1976) could not be further reduced.

Midazolam caused a highly significant increase in slow-wave sleep in healthy volunteers during the first 3 h, when it was detectable in plasma in concentrations of between 150 and 50 ng ml⁻¹. Assessment of the entire night showed that this difference disappeared and all three compounds gave very similar values. In comparison with placebo, midazolam increased slow-wave sleep in the first 3 h and decreased it for the rest of the night. This effect might be regarded as a rebound in the same night. Our data of this normal group demonstrate (see Table 3) that, by dividing the night on the basis of pharmacokinetic behaviour into two parts, a marked difference in the suppression of REM sleep by midazolam is visible. Again, suppression of REM sleep is evident only for the first 3 h while the suppressant effect of oxazepam is present throughout the night.

Therefore it appears that the effects of midazolam on sleep can be related to its pharmacokinetics. Our results also indicate that, dependent on the population studied, different effects of benzodiazepines will be observed on the EEG pattern, and hypnotic efficacies of drugs applicable to insomniacs with established sleep EEG abnormalities (as in this study) can be generated properly only from studies in such patients (Ziegler & Ludwig, 1981).

Midazolam was rated more favourably by the insomniacs than were placebo and oxazepam, while the volunteers noticed no differences. The insomniacs felt that sleep quality was improved significantly after the single-blind switch from oxazepam via placebo to midazolam. We suggest that this favourable subjective rating has its objective correlate in shortened sleep latency.

In conclusion, the short-acting midazolam might be an alternative treatment of functional insomnia, especially if patients suffer from difficulty in falling

asleep. We suggest that a dose of 15 mg of midazolam or even less is clinically effective and safe, since it does not interfere with the patient's daytime activities on the following morning.

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