COMPARISON OF MIDAZOLAM, DIAZEPAM AND PLACEBO IN THE TREATMENT OF INSOMNIA

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SYNOPSIS

A double blind cross over study of midazolam 10 mg, diazepam 10 mg and placebo showed that midazolam was better than placebo in maintaining sleep and was slightly better than diazepam or placebo in terms of shorter sleep latency, fewer night wakenings and longer length of sleep. However more subjects on midazolam complained of feeling less refreshed on wakening compared to those taking diazepam or placebo.

INTRODUCTION

Midazolam is an imidazo-benzodiazepine derivative that like other benzodiazepines has anti-convulsant, anti-conflict and anti-aggressive properties (Pieri L, 1983). (1) What makes it useful for the treatment of insomnia is its strong sedative effect and short duration of action ie half life of 2 hours as compared to 22 hours for flunitrazepam and 8 hours for oxazepam. (Amrein et al, 1983) (1).

In Singapore the most widely used hypnotic is diazepam (Tsoi & Kua, 1984), (3) and so it was decided to carry out a clinical trial comparing midazolam and diazepam to establish whether midazolam would prove superior to diazepam in terms of quick onset of action, more restful and longer sleep, and absence of hangover effects the following day.

METHOD

The subjects were selected from an outpatient group of psychiatric patients aged 22 to 51 years who were not suffering from any psychosis, or serious physical conditions, were not pregnant and had no known allergies to benzodiazepines. All had complaints of poor sleep, with at least one of the following: (a) sleep onset latency of 60 minutes or more, (b) two or more awakenings in the night, (c) early morning wakening and (d) sleep duration of less than 5 hours.

TABLE 1
EXPERIMENTAL DESIGN

4 days	3 days	4 days	3 days	4 days
Midazolam	Placebo	Placebo	Placebo	Diazepam
Diazepam	Placebo	Midazolam	Placebo	Placebo
Placebo	Placebo	Diazepam	Placebo	Midazolam

Table 1 shows the experimental design of the trial. Patients were assigned consecutively to 1 of 3 different designs lasting 18 days during which they took midazolam, diazepam and a placebo for 4 days each. In between were 2 washout periods of 3 days each during which a placebo was given. The 3-day period was required as the half life of diazepam was 20 to 35 hours. The whole trial was double blind. Subjects were seen on the first, eighth and nineteenth days. During the first visit they were administered the Eysenck Personality Questionnaire (Eysenck & Eysenck, 1975) (4), Zung's Self Rating Depression Scale (Zung, 1966) (6), and Zung's Anxiety Status Inventory (Zung, 1971) (5). In addition, they were given post sleep questionnaires to answer daily, 30 minutes after waking up from sleep.

RESULTS

Twenty-four patients completed the trial. There were 12 males and 12 females and the ages ranged from 22 t0 51 years.

Psychological test data

a) Scores on the Eysenck Personality Questionnaire showed that the mean score for extraversion was 8.76, neuroticism, 12.67, psychoticism, 5.96 and Lie, 11.80. (See Table 2)

The subjects, who were all selected from an outpatient psychiatric clinic were significantly more extroverted, neurotic and tough minded than the group of Singapore norms of 85 staff nurses.

b) Scores on the Zung Anxiety Status Inventory showed that the subjects had a mean score of 25.57 and were significantly less anxious than the norms used by Zung ($t = 3.318$, $p < 0.005$, 1 tailed).

c) The subjects who had a mean score on the Zung SDS of 50.05 were moderately depressed. Biggs et al (1978) (7) in comparing the Zung's SDS and the Hamilton Rating Scale for Depression found that those scoring a mean of 49.2 were rated to be moderately depressed on the Hamilton Rating Scale.

Sleep Data

Twenty (83.3%) were unable to fall asleep easily. One (4.1%) had wakeful sleep and 2 (8.2%) woke very early and were unable to sleep again. The mean number of hours spent sleeping was 4.95 hours and the mean sleep onset latency time was 98 minutes.

Sleep parameters

1. Sleep onset latency time

All subjects were asked how long it took them to fall asleep, with the medication viz:-

a) less than 15 minutes = 1
b) between 15-30 minutes = 2
c) between 30-60 minutes = 3
d) more than 60 minutes = 4

The scores of all the subjects on the 4 nights with

TABLE 2
EPQ SCORES OF SUBJECTS AND NORMS

	Subjects (N = 24)		Singapore Norms (N = 85)		
	Mean	SD	Mean	SD	t
Extraversion	8.76	3.82	11.68	4.85	3.1**
Neuroticism	12.67	6.47	9.27	4.64	2.4*
Psychoticism	5.96	4.23	3.6	1.43	2.7**
Lie Score	11.8	4.23	12.53	3.55	.7

** $p < 0.005$ (1 tailed)
* $p < 0.01$ (1 tailed)

TABLE 3
SLEEP ONSET LATENCY SCORES

Medication	Mean	SD
Diazepam	11.25	4.69
Midazolam	9.92	4.01
Placebo	11.08	3.51

each particular medication were totalled (Table 3). Although there was no significant difference in the sleep onset latency between diazepam and midazolam (t = 1.054) and midazolam and a placebo (t = 1.069), midazolam had the shorter mean sleep onset latency time. However a surprising finding was the longer mean sleep onset latency time for diazepam compared to placebo. About 20% of the subjects on midazolam or diazepam slept within minutes, and about 45% of those on diazepam compared to 23% of those on midazolam required more than 60 minutes to fall asleep.

2. Wakenings during sleep

The subjects were scored on the number of times they woke in the night:

no interruption of sleep = 1
1 to 2 awakenings = 2
3 or more awakenings = 3

TABLE 4
NIGHT WAKENING SCORES

Medication	Mean	SD
Diazepam	7.38	2.57
Midazolam	6.58	2.25
Placebo	8.12	2.17

The scores were totalled for all 4 nights. The higher the score, the more interrupted the sleep. (See Table 4)

There was no significant difference in the mean score between diazepam and midazolam but midazolam produced significantly less wakening per night than placebo (t = 2.41 p 0.01). Of the 3 substances, midazolam produced the least number of wakenings per night.

About 46% of those on midazolam did not have any wakening at night compared to 36% on diazepam and 23% on placebo.

3. Length of sleep

Subjects were scored on the number of hours they thought they slept and the scores were:

9 hours or more = 1
6 to 8 hours = 2
4 to 5 hours = 3
3 hours or less = 4

The scores were totalled for the 4 nights. The lower the score the longer the subject felt he slept.

There was no significant difference in the length of sleep between diazepam and midazolam (t = 1.367), and between midazolam and placebo (t = 1.221). But subjects on midazolam had the longest mean length of sleep and those on diazepam the shortest. Of the subjects who slept more than 6 hours, about 60% of them were on midazolam as compared to about 50% on diazepam.

TABLE 5
LENGTH OF SLEEP SCORE

Medication	Mean	SD
Diazepam	10.17	3.03
Midazolam	9.13	2.23
Placebo	9.92	2.26

4. State on waking from sleep

Subjects were scored on how they felt in the morning on a 3 point scale, from 1 for refreshed to 3 for very unfreshed. Thus the lower the score, the more refreshed the subject felt. The scores for the 4 nights were added and the mean obtained. (Table 6).

TABLE 6
STATE ON WAKING SCORES

Medication	Mean	SD
Diazepam	6.83	2.20
Midazolam	7.37	2.10
Placebo	7.25	2.31

There was no significant difference in the state on waking scores between diazepam and midazolam and between midazolam and placebo. However subjects felt most refreshed after taking diazepam and least refreshed after taking midazolam.

About 42% of those on diazepam felt refreshed on waking compared to 35% of those on midazolam, and about 20% of those on midazolam (19.7%) felt very unrefreshed compared to 12% on diazepam.

DISCUSSION

The results indicated that there was no significant difference between diazepam and midazolam on all the sleep parameters and also between midazolam and placebo except on the night wakening score, which showed that those on midazolam had significantly fewer wakenings than those on placebo. However, those on midazolam had shorter sleep onset latency, fewer night wakenings, and longer length of sleep compared to those on diazepam or placebo, although the results did not reach statistical significance. Many studies have shown midazolam to be better than other hypnotics. Gallais et al (1983), found in a parallel trial comparing midazolam with oxazepam and a placebo that sleep onset latency was significantly shorter with midazolam. Feldmeier & Kapp (1983) (8) also comparing midazolam with oxazepam obtained a shorter sleep onset latency and more favourable patient response with midazolam. In addition, Fischbach (1983) (9) noted that midazolam lengthened the sleep duration more than oxazepam. Although Phillip & Kapp (1983) (10) obtained no difference between midazolam and Vesparax (hydroxyzine 50 mg, secobarbital 150 mg and allobarbital 50 mg) in hastening sleep onset, increasing sleep duration and

improving sleep quality, Lachnit et al (1983) (11) found Vesperax to have more side effects.

In this study midazolam proved to be worse than diazepam in terms of the waking state. More subjects felt unrefreshed and tired. It is difficult to explain this finding, as the dosage of midazolam (10 mg) was on the low side and the half life is short compared to that of diazepam, and other studies have shown that patients are alert and do not suffer hangover effects the morning after taking midazolam. Nicholson & Stone (1983) (12) found that patients on midazolam 10 mg, 20 mg or 30 mg did not show any impairment on tests of digit symbol substitution 9 hours after ingestion, while Gudgeon & Hindmarch (1983) (13) found that the sedative effects of midazolam at 15 mg and 20 mg had dissipated after 7 hours of ingestion, using test measures of choice reaction time, critical flicker fusion and a visual analogue scale measuring tiredness, drowsiness, alertness, clumsiness and dizziness.

CONCLUSION

A double blind cross over study of midazolam 10 mg, diazepam 10 mg and placebo showed that midazolam was better than placebo in maintaining sleep and was slightly better than diazepam or placebo in terms of shorter sleep latency, fewer night wakenings and longer length of sleep. However more subjects on midazolam complained of feeling less refreshed on wakening compared to those taking diazepam or placebo.

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