MIDAZOLAM DOSAGE STUDIES IN INSTITUTIONALIZED GERIATRIC PATIENTS

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1 Three different dosage studies were carried out with midazolam in 47 institutionalized geriatric patients (17 males: mean age 82.9 years; 30 females: mean age 81.3 years) who were suffering from insomnia of long standing.

2 Study I investigated the hypnotic efficacy of midazolam versus placebo in a double-blind, cross-over trial comparing the 7.5 and 15 mg doses of midazolam in 18 subjects. Both midazolam doses shortened sleep onset latency by 40 min (15 mg) and 31 min (7.5 mg). Both doses increased total sleep time compared with placebo.

3 In study II, a comparative, cross-over trial in 10 subjects, an initial dose of 7.5 mg midazolam was sufficient to reduce the subjective appreciation of sleep onset time to < 60 min on 66 of 70 study nights. Oxazepam (25 mg) had a comparable favourable effect but less frequently (53 of 70 nights).

4 In study III, individual dose limits were investigated in 19 insomniac patients. The minimum effective dose was 7.5 mg. The maximum tolerated dose was in the range 15 to 52.5 mg according to the subjects' assessment. The most common optimum dose was 15 mg (10 of 19 patients). The higher doses prolonged sleep but midazolam appears to have a wide margin of safety as residual sedative effects appeared only after very high doses (four of 19 for 30 mg; eight of 19 for 37.5 mg). In some patients, 7.5 mg was the minimum dose that was effective in shortening sleep latency. The standard dose, i.e. 15 mg, however, does not seem to differ from that for younger adults, this dose being effective in most patients in shortening sleep latency, reducing the number of awakenings and prolonging sleep, and does not appear to have residual effects in the morning after awakening.

Introduction

Treatment of insomnia is an important part of the overall management of hospitalized geriatric patients. In our geriatric ward, 10% of our patients suffer from difficulty in sleeping. The causative factors in insomnia, however, are usually not known and, in practice, they are rarely dealt with effectively.

The most common type of sleep disorder is a difficulty in falling asleep which usually necessitates taking a hypnotic at bedtime. The fear of being unable to fall asleep often leads to excessive demands on the part of the patient thus afflicted, especially in a hospital setting in which unfamiliar surroundings and the nursing required by invalids during the night will result in frequent disturbances of sleep. We verify the need for a hypnotic by administering placebo for 2 consecutive nights, this period being extended to facilitate withdrawal of the medication if the substitution by placebo shows that the insomnia is not genuine.

Benzodiazepines are favoured in such a context because of their anxiolytic, sedative properties and particularly because of their safety which is superior to that of chloral hydrate or barbiturates (Goldson,

1981). However, benzodiazepines with a long half-life have been criticized for causing residual sedative effects capable of reducing vigilance on the following morning, particularly in high doses to which the elderly are more sensitive (Reidenberg *et al.*, 1978; Greenblatt & Allen, 1978; Castleden *et al.*, 1977).

For this reason, combined with the fact that benzodiazepines are extremely potent, these drugs should initially be administered in low doses with gradual increase towards effective levels in order to gauge the individual sensitivity of the patient. The use of a benzodiazepine with a short half-life such as oxazepam or triazolam might theoretically facilitate dosage titration in elderly patients (Devenyns, 1981). However, the data available from comparative studies show no significant differences with regard to side-effects, at least in moderate dosages (Reeves, 1977; Okawa, 1978).

We conducted 3 studies with midazolam, a benzodiazepine with a biological half-life of only 1.3–2.2 h (Brown *et al.*, 1979). The common aim of these studies was to investigate the dose range in which

midazolam would exercise sufficient hypnotic effect without residual effects influencing morning awakening.

For younger adults, i.e. non-geriatrics, a dose of 10–20 mg of midazolam has been reported as optimal (Lupolover & Buch, 1981). In subsequent studies, a standard dose of 15 mg has been used. In the first study of this 3-part investigation, the aim was to determine the minimum and optimum effective dose in geriatric patients. The second study was designed to study the efficacy of midazolam in an initial dose of 7.5 mg compared with oxazepam. The aim of the third study was to determine the dose limits of midazolam in long-stay hospital patients who had been previously treated with hypnotics.

Methods

Patients

Patients were selected from amongst a hospitalized geriatric population. The main prerequisite for inclusion was preservation of the mental faculties so that the subjects could provide reliable responses to the tests of efficacy.

Protocol

Study I This study was conducted using a double-blind cross-over procedure in 18 subjects suffering from nocturnal awakenings. In random order, the subjects received 7.5 mg midazolam (1 night), 15 mg midazolam (1 night) or placebo (1 night). Thus there were 6 possible sequences, with three subjects per sequence. The tablet was administered if the patient awoke during the night between 23.00 and 01.00 h, i.e. 3–5 h after going to bed. The same nursing team supervised tablet administration and assessed sleep onset and the total sleep duration until 07.00h. (Patients are usually woken at 07.00 h when the day staff take over). The supervising physician examined the patients for signs of excessive sedation between 09.00 and 11.00 h.

Study II This study was also conducted double-blind. The 10 subjects studied were suffering from previously treated insomnia. In a cross-over design and in random order (two series of five cases each), patients received midazolam or oxazepam each night for 7 days.

The unmarked tablets contained either 50 mg of oxazepam or 15 mg of midazolam. One half-tablet was given as the initial dose at bedtime and the second half given after 1 h if the patient had not fallen asleep. All patients received placebo (single-blind) for 2 consecutive nights at the start of the study, between the 2 verum periods and at the end of the study. A good

night's sleep with placebo ranked as grounds for exclusion. Sleep onset and duration were monitored by the night nurse who checked the patient at 10-min intervals until sleep onset and once per hour thereafter. The physician obtained the patient's opinion and evaluated the degree of sedation in the morning between 09.00 and 11.00 h.

Study III This was carried out as an open study in 19 patients. On the first 4 nights, patients received a placebo identical in appearance to their previous hypnotic. Midazolam was then started, initially giving the same dose, in terms of number of tablets, as the previous hypnotic, i.e. half or one tablet. Every 2 nights, the dose was increased by one half-tablet and the patient carefully monitored until signs of excessive sedation were evident on awakening.

When this point was reached, the doses were gradually decreased again in the same way by ½-tablet every second night, to the level at which the dose was judged insufficient. The patients were monitored by the night staff and seen by the physician in the morning, as in study II.

Statistical analysis

The values for sleep onset latency and total sleep duration were subjected to analysis of variance, taking into account intra-individual variability (in case of repetition) and inter-individual variability, variability between periods (sequence as a factor), compounds and doses. The Student *t* coefficient for paired series was calculated. However, sleep latency as it was registered can be considered as a non-continuous variable so that the validity of the conclusions was verified by non-parametric tests: the Mann-Whitney test for comparison between treatments and the Wilcoxon test for between-series comparison in study II.

Results

Patients: type of insomnia and concomitant medication

Table 1 outlines the basic information relating to the type of insomnia: organic illness was the cause of insomnia in six of 18 patients in study I. In the other cases, some degree of anxiety was manifest; insomnia was of long standing and previously treated in most cases (42 of 47); insomnia was associated with numerous illnesses leading to loss of autonomy and to hospitalization. The protocol excluded patients receiving psychotropics but accepted patients receiving long-term treatments that could not be interrupted. In this population of 47 patients, 75 different compounds were being administered concomitantly.

Table 1 Characteristics of insomnia of patients in the three studies

Item	Study I	Study II	Study III
<i>n</i>	18	10	19
Organic origin	6	0	0
Chronicity in months ($\bar{x} \pm \text{s.d.}$)	25 ± 30	41 ± 44	51 ± 59
Already receiving a hypnotic	14	10	18
With associated illness(es)	17	9	18
Number of other medications (no psychotropics)	29	18	28

The study population consisted of 17 males (mean age 82.9 years) and 30 females (mean age 81.3 years).

Study I

The tablet was administered on demand between 23.15 and 0.45 h (mean 23.44 ± 0.20 h). Table 2 lists the values for sleep onset latency and total sleep duration. After administration of 7.5 mg midazolam, there was a trend ($P < 0.1$) towards a faster return to sleep. After 15 mg midazolam the latency for falling asleep again was reduced compared with placebo ($P < 0.05$) by mean 40 min.

Both midazolam doses significantly increased the total sleep duration compared with placebo. Sleep was increased by 1.16 h with midazolam 7.5 mg ($P < 0.05$) and by 1.27 h by the higher dose ($P < 0.02$).

No residual effect was detectable in the morning following administration of 7.5 or 15 mg midazolam between 23.00 and 01.00 h.

Study II

The results obtained in this study for sleep onset latency and total sleep duration are presented in Table 3.

The mean sleep onset latency was 20.8 min shorter with midazolam than with oxazepam ($P < 0.05$). There was also a greater variability for this value amongst the subjects receiving oxazepam.

Midazolam in a dose of 7.5 mg was more effective in shortening sleep latency than was 25 mg oxazepam. The second half-tablet of midazolam, bringing the total dose up to 15 mg, was required on only 4 of 70 nights whereas, in the case of oxazepam, the second half tablet (25 mg) was necessary on 17 of 70 nights; this difference between the 2 compounds is significant ($P < 0.01$). Thus, the mean dose per night was 7.9 mg for midazolam and 31.1 mg for oxazepam.

There was a trend ($P < 0.1$) towards a longer mean total sleep duration under midazolam (8.3 h) than after oxazepam (7.5 h).

Study III

Details of the dosage adjustment are summarized in Table 4 and Figure 1.

The initial dose, the same in terms of tablet number as the hypnotic previously taken, was one half-tablet in three patients and 1 tablet in 16 cases. Dosage increase to a level of excessive sedation led to doses in the range of 1½ tablets (one case) to 4 tablets (three cases), with the mean dose 2.9 tablets, i.e. 43.5 ± 11.25 mg. The mean maximum tolerated dose was one half-tablet less than the mean maximum dose attained (mean 36 ± 11.25 mg).

The optimum dose (Table 4) was close to the minimum effective dose of one half-tablet in nine cases and 1 tablet in 10 cases.

Table 2 Study I: Sleep onset latency and total sleep duration after placebo, 7.5 mg midazolam and 15 mg midazolam administered in cases of nocturnal awakenings in 18 patients (mean sleep duration before awakenings = 1.24 ± 1.04 h).

Parameter	Placebo	Midazolam (7.5 mg)	Midazolam (15 mg)
$\bar{x}$ sleep latency after nocturnal awakening in min ($\pm \text{s.d.}$)	86.9 ± 7.10	55.8 ± 66.2	46.7 ± 22.6
difference to placebo	—	$-31.1 \pm 74.9^*$	$-40.2 \pm 70.6^{**}$
$\bar{x}$ sleep duration after nocturnal awakening in h ($\pm \text{s.d.}$)	3.76 ± 2.27	4.92 ± 2.37	5.04 ± 1.86
difference to placebo	—	$+1.16 \pm 2.14^{**}$	$+1.28 \pm 2.09^{***}$

* $P < 0.10$; ** $P \pm 0.05$; *** $P < 0.02$ v. placebo, Student's paired *t*-test.

Table 3 Study II: doses (means and ranges), sleep onset latency and sleep duration for oxazepam and midazolam ($n = 10$)

Parameters	Oxazepam	Midazolam	Differences
Mean dose (range) in mg	31.1 (25–50)	7.9 (7.5–15)	—
Mean sleep onset latency in min ($\pm$ s.d.)	64.1 $\pm$ 14.7	43.3 $\pm$ 10.5	20.8 $\pm$ 27.8**
Mean sleep duration in h ($\pm$ s.d.)	7.52 $\pm$ 0.96	8.3 $\pm$ 0.98	0.51 $\pm$ 0.85*

* $P < 0.1$; ** $P < 0.05$ between oxazepam and midazolam, Student's paired t -test.

Figure 1 Dose limits established in study III ($n = 19$): minimum effective and maximum tolerated doses. Dosage was increased by 7.5 mg every second night until the maximum tolerated level was reached, and then decreased again to find the minimum effective dose. Each column represents the mean value for 2 days. The number at the top of each column represents the number of patients to receive this dose. The dose effect is expressed in terms of sleep duration. The evolution of dose effect during the study can be seen by comparing identical doses during the ascending and descending phases.

Discussion

Problems connected with dosage are especially important in the treatment of geriatric patients. Where treatment with a hypnotic is indicated, it is necessary to avoid excessive sedative effects by initially selecting the lowest possible effective dose. In this study, the minimum effective dose of midazolam ranged from 7.5 to 15 mg and approximately corresponded to the optimal dose, defined as a dose which can be satisfactorily administered over a period of several months, as is the case with the 19 subjects of study III which is still in progress for the purpose of long-term evaluation.

In certain patients, the wish to 'sleep well' equates with the desire to sleep as long as possible without experiencing difficulties on awakening. The maximum midazolam dose tolerated without any lingering effect on normal daytime activities was found to vary greatly between individuals and was in the range 1 to 3½ tablets (15–52.5 mg). After high doses, especially 3 tablets or more, sleep often lasted 10 h. This duration was regarded as satisfactory by the majority of the patients, this being understandable in view of the sleeping times timetabled by the institution (20.00–07.00 h). Spontaneous sleep lasting 10 h or more is rare in 80-year-old subjects. Thus, the sleep duration obtained with high doses of midazolam (≥ 30 mg) was longer than that expected for this age group. As the 'normal daytime activities' of the subjects in

Table 4 Study III: ($n = 19$): results of dosage adjustment (increase or decrease by 7.5 mg midazolam every 2 days). Doses ascending to tolerance limit, then decreasing to the optimal dose (figures refer to number of subjects)

Dosage level (no. tablets)	Initial dose	Maximum dose attained	Maximum dose tolerated	Optimum dose	Minimum dose effective
0.5	3	—	—	8	9
1.0	16	—	1	10	10
1.5	—	1	3	1	—
2.0	—	3	4	—	—
2.5	—	4	4	—	—
3.0	—	4	4	—	—
3.5	—	4	3	—	—
4.0	—	3	—	—	—
No. tablets					
$\bar{x} \pm$ s.d.	0.92 $\pm$ 0.19	2.92 $\pm$ 0.75	2.42 $\pm$ 0.75	0.82 $\pm$ 0.30	0.76 $\pm$ 0.26

the context of the studies reported here are not overly demanding in terms of alertness or performance, impairment of these functions would have to be marked before becoming noticeable to the patients or to those around them. For this reason, some degree of residual effect of the highest doses cannot be excluded. As demonstrated by our studies, administration of high doses of midazolam is possible but would be successful or appropriate only in exceptional cases.

These three dosage studies in geriatric patients showed midazolam to be effective against difficulties in falling asleep when given in the standard dose of one half or 1 tablet. Increasing the dose can markedly

lengthen the total sleep duration by several hours with a moderate risk of residual sedative effects in the morning.

The marked inter-individual variability in sensitivity to hypnotics makes it necessary to titrate dosage for each patient individually. As shown by our study, one half tablet (7.5 mg) of midazolam is the minimum effective dose and is sufficient to induce sleep in some patients. The total sleep duration will, however, be increased when the dosage is raised. A regularly administered dose higher than 1 tablet (15 mg) seems to be indicated only in exceptional cases.

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