MIDAZOLAM AND TRIAZOLAM IN OUT-PATIENTS: A DOUBLE-BLIND COMPARISON OF HYPNOTIC EFFICACY

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1 The hypnotic efficacy and the effect on the condition after morning awakening of midazolam 15 mg and of triazolam 0.5 mg were studied in a multicentre, double-blind cross-over study in 198 out-patients with sleeping difficulties of various origin.

2 The subjects received each drug for two consecutive nights, and completed a questionnaire each day on awakening.

3 Both midazolam and triazolam significantly shortened the sleep-onset latency, reduced the number of awakenings, and increased the total sleep time.

4 The state on awakening was also significantly improved after both compounds for several self-rated items. There was a difference only with regard to the patients' feeling of being under drug influence, which was reported as being significantly more marked after triazolam.

5 In conclusion, both compounds were effective and well tolerated in the doses used, only a few side-effects being reported.

Introduction

In normal individuals, sleeping patterns vary from person to person; these variations occur in the same individual according not only to the different phases of his life, from childhood to old age, but also in relation to the degree of physical or mental activity performed. Undesirable changes in the sleeping pattern are common and are equally as frequent in hospitalized patients as in out-patients. The underlying reasons for sleeping problems are very important: the schizophrenic patient may be too disturbed to sleep; the senile patient is usually confused and will mistake night for day in troubled agitation; the obsessive patient will worry about compulsive rituals; the maniacs will be excessively busy and active; the depressed may wake up too soon, already involved in nihilistic thoughts. In morbid anxiety, the initial symptom is often sudden awakening in the early hours of dawn, in a state of near panic. Emotional tension can manifest itself in the complex motor activity of somnambulism in predisposed subjects. An abnormality in sleep rhythms is present in certain cases of mental deficiency. A reversion in sleep rhythms can be found in patients suffering from a hypophysis tumour. Prevented from normal sleep, the most well-balanced mind will soon present abnormal psychological symptoms that are extraordinarily similar to those of serious mental illness.

Sleep may be disturbed by a wide variety of somatic illnesses. Localized pruritus—a feature of several cutaneous afflictions—is often exacerbated by bed-warmth and makes it difficult for the patient to fall asleep. The pain associated with hiatus hernia will prevent sleep or awaken the patient soon after he has fallen asleep, while the discomfort of duodenal ulcer may delay sleep until after midnight or even early morning. Dyspnoea in patients with heart failure will either keep the patient awake or allow him at best only light and unsatisfactory sleep, particularly when recurrent Cheyne–Stokes attacks are a feature. Angina pectoris sufferers may also be awoken by a night-time episode. Prostatic hypertrophy or cough of various origin will also frequently interrupt sleep. Hyperthyroidism and chronic infections may also be accompanied by distressing and long-lasting sleeplessness.

In all these instances, the primary concern is to treat the cause of insomnia. However, many patients will also require a hypnotic during the critical phase. In hospitalized patients, sleeping problems are often related to organic or psychiatric illness. The insomnia of out-patients is often psychogenic in origin or is due at least in part to stimulants, heavy meals, or environmental disturbances. Thus sleep disorders in ambulant patients differ in their aetiology, sometimes quite

markedly from those in hospitalized patients. Various authors (du Cailar *et al.*, 1983; Gallais *et al.*, 1983) have reported favourable results with midazolam in the treatment of insomnia of hospitalized patients. We therefore decided to compare midazolam in out-patients with triazolam, a compound with a similar profile of action, given in the dosage of 0.5 mg, the usual dose in Brazil.

The four centres taking part in the multicentre study treat quite different patient groups, i.e. neurological, psychiatric, general medical and internal medicine cases. Thus, the study population offered a fairly representative cross-section of insomnia in out-patients.

Methods

The study was performed on four consecutive nights according to a cross-over schedule. One group of patients received 15 mg midazolam for two nights and 0.5 mg triazolam for the following two nights. The other group received the same compounds in the reverse order. The subjects were allocated to the two groups according to a randomization list, and the drugs were administered following a double-blind procedure. In the morning after each drug administration, the patients filled in a questionnaire in which they assessed the time taken to fall asleep, the number of nocturnal awakenings, the total sleep duration (in hours), and how they felt in the morning 30 min after getting up. After the second and fourth nights, they also answered more detailed questions concerning their physical and mental condition in the morning (1000–1100 h), assessing this according to a nine-item visual analogue scale (Table 1) which has been found reliable in other investigations (Ziegler *et al.*, 1983; Amrein *et al.*, 1979). At the end of the study, the subjects were asked to indicate whether they had slept better on night 2 or on night 4, i.e. after midazolam or after triazolam.

The study was carried out in a patient population with sleeping difficulties of various origin, and included subjects of both sexes in the age range of 20 to 60 years. To qualify, a patient had to have at least one of the following symptoms: sleep-onset latency longer than 30 min, two or more awakenings during the night (broken sleep), premature morning awakening, sleep duration of less than 6 h, no response to one tablet of a standard hypnotic.

The objectives of the study as well as the properties of the drugs to be used were explained to the patients, and their consent to participate was obtained.

The following were automatically excluded: pregnant women and female patients without adequate contraceptive protection; patients in poor general condition, or with neurologic, haematologic, hepatic, renal, cardiovascular, or other serious de-

compensated illness; those with a known allergy to benzodiazepines; subjects with severe psychosis or psychoneurosis; patients requiring concomitant intake of other psychotropic agents such as tranquilizers, neuroleptics, antidepressants, analgesics and/or alcohol; patients with severe acute or chronic pain. The study was to be interrupted on the appearance of illness with high temperature, gastrointestinal disorders, severe pain, or the need for psychotropic agents or analgesics.

Where appropriate, the contingency tables were evaluated by means of the χ^2 test or the McNemar test. The scores on the visual analogue scale were assessed in terms of the distance from the left-hand end of the scale. The difference between the two tests was calculated and analysed using the Wilcoxon test for paired differences. To obtain an overall assessment, the individual items were added, according to their meaning (inversion of items 2, 4, 6, 8, 9) and the difference analysed again by Wilcoxon test.

Results

Patient population

A total of 198 out-patients (105 males and 93 females) entered the study, and 197 completed it. The subjects' mean height was 165.6 cm, their mean age was 41.7 years, and their mean weight was 65.7 kg. Ninety-five patients (52 males and 43 females) received midazolam for the first two consecutive nights and triazolam for the last two consecutive nights; 103 patients (53 males and 50 females) received triazolam for the first two nights, followed by two nights with midazolam.

One hundred and thirty patients were under treatment for various internal disorders, mainly cardiovascular in nature. Their sleeping difficulties were mostly psychogenic or situational in origin. Forty patients were psychiatric outpatients being treated at a university clinic. These patients were suffering from affective neurosis or psychosis with remission of symptomatology. They were all receiving psychotherapy, and the administration of psychotropic substances was stopped at least one week before the start of this study.

Twenty-seven patients were receiving out-patient treatment at a neurology clinic.

Before treatment, 149 patients complained of difficulty in falling asleep, 86 of broken sleep (several awakenings during the night), 92 patients reported sleeping less than 6 h each night, and 101 complained of premature awakenings. However, these symptoms did not usually occur alone, and were usually found in combination: 33 patients featured all four symptoms, 42 patients had three of the four symptoms, 49 had two and 74 had only one. Of this latter group, 43 had difficulty in falling asleep, 14 awoke prematurely,

Item	Relative improvement	p ≤	
		0.1	0.05
1 wakefulness	11%	●	
2 muscle strength	5%
3 relaxation	10%	●	
4 concentration	16%	●	●
5 general well-being	11%	●	●
6 activity	8%
7 sociability	2%
8 mood	7%
9 perceived drug effect (improvement = decrease)	11%
Mean score	12%	●	●

Table 1 Improvement in self-rated items during course of treatment (comparing morning after night 4 with that after night 2). All scores obtained 12 h after drug administration

eight had disturbed sleep with awakenings, and nine had short sleep duration. This distribution is typical for insomnia: amongst the group featuring only one symptom, a difficulty in falling asleep was the most common. Overall, however, sleep disturbances were expressed more frequently in terms of a combination of symptoms.

Effects on sleep

On the first night of the study, 70% of the patients fell asleep within 40 min; on the fourth (last) day, the corresponding figure was 78% (Table 2). The two compounds were very similar in effect (73% favourable results for midazolam, 68% for triazolam on the first night). The frequency of awakening was reduced to about the same extent by both drugs, and total sleep duration increased. For all three parameters, the improvement over baseline was highly significant (McNemar test, $P < 0.01$). There was also a trend ($0.05 < P < 0.1$) towards further improvement of sleep parameters during the four-day therapy. This apparently slight additional improvement had a marked effect on the patients' condition. Regardless

of the order in which the different compounds were administered, the patients felt better able to concentrate (Wilcoxon test, $P < 0.05$), had an improved general condition ($P < 0.05$), were more relaxed ($P < 0.1$) and more refreshed ($P < 0.1$) on the morning after the fourth night than after the second night. Other scales also showed favourable quantitative changes (increased activity drive, improved mood, 'in better form') which contributed to an improvement ($P < 0.05$) in the total score (Table 1).

In eight of nine self-rating scales completed by the patients, the effects of both midazolam and triazolam on the state on morning awakening were assessed by the patients as being similar. However, on the morning following triazolam administration, patients reported feeling more strongly under drug influence than after midazolam (McNemar test, $P < 0.1$). With regard to other side-effects, one patient complained of a dry mouth after midazolam. After triazolam, one case each of slight vertigo, mild nausea, slight somnolence, and marked somnolence were reported. After both drugs, there were three complaints of tremor and two of vertigo, although these were possibly manifestations of the primary illness rather than drug-induced side-effects.

Table 2 Sleep before and during treatment (M, midazolam; T, triazolam)

Parameters	Baseline Total	Night 1			Night 4*		
		Total	M (%)	T (%)	Total	M (%)	T (%)
Sleep-onset latency							
< 40 min	52	139	73	68	153	79	76
> 40 min	146	59	27	32	44	21	24
Number of awakenings							
0-2	112	176	89	89	186	93	93
> 2	86	22	11	11	11	7	7
Total sleep duration							
> 6 h	106	170	86	85	179	89	93
< 6 h	92	28	14	15	18	11	7

* One patient did not complete the study (failed to reappear).

Discussion

This study in out-patients largely confirmed the findings in hospitalized patients. On the first night, midazolam and triazolam both had a favourable effect on sleep-onset latency, number of awakenings, and sleep maintenance. The effect of the standard dose of midazolam (15 mg) is about the same as that of 0.5 mg triazolam, a dose which today is being increasingly regarded as the maximum dose. For hospitalized patients, residual effects on the following day play a less important role. Persistence of a slight sedative effect is usually acceptable or even desirable. The situation, however, is different in out-patients who work, and for whom a rapid transition from sleep to wakefulness is absolutely essential. For such patients, the ideal hypnotic provides rapid sleep onset and undisturbed sleep, but does not result in performance decrements on the following morning. Patients who have slept badly or not at all will show a decline in performance scores on the following morning. It is therefore conceivable that effective treatment with a hypnotic could in fact appear to improve performance on the following day. The favourable effect of 15 mg midazolam and of 0.5 mg triazolam on sleep parameters, particularly on sleep-onset latency, has been well established. For both substances, residual effects and the influence on performance have been carefully and thoroughly investigated.

Studies at several centres, using different methods (Gudgeon & Hindmarch, 1983; Hauri *et al.*, 1983; Nicholson & Stone, 1983; Vogel & Vogel, 1983; Ziegler *et al.*, 1983), have shown that, following 15 mg midazolam, performance scores will run in parallel to the sedative effect, showing impairment (at its maximum 1-2 h after ingestion) followed by a gradual return to baseline values 4-5 h after drug intake. The findings after administration of 0.5 mg triazolam are less consistent. Veldkamp *et al.* (1974) reported no

marked hangover effect. This finding has been questioned, however, by Chick (1980). Furthermore, recent papers have reported a marked impairment of early morning performance (Hindmarch & Clyde, 1980; Nicholson & Stone, 1980; Mattmann *et al.*, 1982) following administration of 0.5 mg triazolam. Our study confirmed this finding. Twelve hours after triazolam administration, patients still reported a 'drugged feeling', although at the same time point after midazolam ingestion, this was absent. In this self-rating scale (Table 1), which experience has shown to be a very sensitive and reliable detector of residual effects, the two compounds differed to a statistically highly significant degree. On the other hand, on continuing treatment, regardless of whether they were receiving triazolam or midazolam, the patients reported an increasing improvement in several variables concerning general condition. This can be ascribed at most only partially to residual pharmacological effects, and it appears likely that this is the consequence of an undisturbed and restorative sleep. We know from subjective experience that our daytime condition and performance will largely reflect how we have slept the night before. The results of our studies are in agreement with this experience.

The 'drugged feeling' reported at 12 h after drug ingestion had a decreasing tendency ($P \sim 0.1$) during the course of treatment, confirming the experience that, even after a relatively brief period of treatment with benzodiazepines, unwanted effects frequently disappear as a result of adaptive or compensatory mechanisms.

The results obtained at the individual centres participating in this study did not significantly differ from one another. Both midazolam and triazolam were effective in treating insomnia of many different origins. However, the triazolam dose should be reduced to avoid side-effects such as somnolence and vertigo.

In summary, both midazolam and triazolam in the

doses used in this study were well tolerated and were equally effective in shortening sleep-onset latency,

increasing total sleep duration, and improving both sleep quality and the state on awakening.

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