EFFICACY AND SAFETY OF MIDAZOLAM AND VESPARAX IN TREATMENT OF SLEEP DISORDERS

R. FISCHBACH

Landesnervenklinik, A-5020, Salzburg, Austria

1 In a double-blind parallel study in which a placebo phase preceded and followed the double-blind verum phase, midazolam 15 mg and Vesparax (150 mg secobarbital, 50 mg brallobarbitol, 50 mg hydroxyzine) were administered to 30 female patients aged 20–76 years, suffering from insomnia secondary to neuromuscular disease.

2 Both products were shown to be efficient hypnotics maintaining a constant level of effect. Midazolam proved to be better tolerated and, in contrast to Vesparax, did not cause hangover, nor did rebound phenomena ensue after its withdrawal.

Introduction

The results obtained in open trials and confirmed in double-blind studies have shown midazolam to be very effective in the treatment of sleep disorders of different degree (Lupolover & Buch, 1981; Scollo-Lavizzari, 1983; Vogel & Vogel, 1983). In comparative studies with other benzodiazepine derivatives, midazolam has frequently been shown to be superior to the reference compounds, particularly with regard to diminishing the sleep onset latency (Helcl *et al.*, 1981; Feldmeier & Kapp, 1983; Nicholson & Stone, 1983).

Vesparax (150 mg secobarbital, 50 mg brallobarbitol, 50 mg hydroxyzine) is a fast-acting hypnotic agent with a reliable therapeutic effect. However, barbiturates are shown to possess certain disadvantages such as loss of effect with frequent use, development of habituation or dependence, and a narrow margin of safety. We thus decided to compare midazolam with a preparation containing barbituric acid to determine whether this benzodiazepine possesses the desirable therapeutic properties of the barbiturates but without their disadvantages.

Methods

Patients

The efficacy and safety of orally administered midazolam and Vesparax were compared in 30 hospitalized female patients suffering from insomnia secondary to neuromuscular disorders. Only patients who spontaneously requested hypnotic medication were included in the study. Pregnant women, patients in poor general condition, and those suffering from severe psychoses or psychoneuroses were excluded.

In accordance with the Declaration of Helsinki, the patients were informed about the trial and their consent to participate obtained.

Study design

The study extended over 9 nights. The first 2 nights were planned as a single-blind placebo phase to determine the degree of insomnia and to exclude strong placebo reactors. This was followed by a 5-day double-blind phase with parallel comparative groups (nights 3–7) and subsequently a 2-day withdrawal phase (nights 8 and 9) when placebo was again administered. Placebo, midazolam, and Vesparax were made available in identical forms and were to be given in a fixed dose of one tablet each night. Group allocation was made according to a computer-generated randomization list with blocks balanced after 10 patients.

Parameters measured

The following *sleep parameters* were observed: sleep onset latency, total sleep duration, awakenings, state on morning awakening, overall assessment by the patient and by the physician.

Sleep latency was assessed by having the night staff check the patients 20, 40, and 60 min after administration of the drug. Patients were then checked again at 2 h intervals for the registration of awakenings. The time of morning awakening was also noted by the hospital staff.

Each morning on awakening, the patients were asked about their subjective state.

Margin of safety: therapeutic index

The margin of safety for both treatments was determined by calculating the proportional factor Q_{TI} . This is obtained by dividing the number of nights with favourable therapeutic effect (sleep onset within 20 min) by the number of nights followed by hangover or side-effects:

$$Q_{TI} = \frac{\text{nights with good therapeutic effect}}{\text{nights with side-effects}}$$

The higher this index, the more favourable is the assessment of the compound's therapeutic effect.

Safety data

Laboratory tests of liver function (enzymes), blood count, serum electrolytes, creatinine, fasting blood sugar, urea and renal function were carried out for all patients before and after administration of the active medication.

Results*Study population*

A total of 30 hospitalized female patients (age range 20–76 years; weight range 45–92 kg; height range 156–178 cm) suffering from insomnia secondary to neuromuscular disease were included in the study. Fifteen patients received midazolam and an equal number received Vesparax.

To make the study correspond as closely as possible to real conditions, patients were not selected according to the type of insomnia. About half complained mainly of difficulty in falling asleep, while the rest were suffering from disturbed sleep with unpleasant dreams. Almost none of the subjects were sleeping more than 6 h (Figure 1). The two treatment groups did not differ with regard to the baseline values for the parameters measured ($P > 0.1$).

Sleep onset latency

During the initial placebo phase, all patients required more than 20 min to fall asleep (Figure 1). On the first night on which midazolam was given, there was a marked shortening of the latency period: only one of the 15 patients did not fall asleep within 20 min. This favourable effect on sleep onset was maintained for all 5 nights and the improvement was highly significant ($P < 0.005$). Vesparax also induced a marked improvement of sleep latency, although on each night 20–33% of the patients required more than 20 min to fall asleep. Thus, midazolam was somewhat more effective ($P < 0.1$) than Vesparax in reducing sleep latency (Figure 2).

Figure 1 Sleep pattern on night 2 (second placebo night). Values represent baseline.

During the concluding withdrawal phase, sleep onset latency again increased compared with the treatment period in all cases. In the midazolam group, however, the latency period on both withdrawal nights remained somewhat shorter than in the placebo selection phase, around 80% of the patients falling asleep within 40 min. In the Vesparax group, about half of the patients fell asleep within 40 min on the first withdrawal night but on the second withdrawal night, only one-third fell asleep within this time-span.

Figure 2 Sleep latency: evolution during study. The values represent the percentage of patients with a sleep latency of longer than 20 min. As can be seen, there was a marked drop in both groups, particularly in the midazolam group, during the verum phase, with a return to baseline values during the withdrawal phase.

Total sleep duration

During the initial placebo phase, mean total sleep duration was 5 h (Figure 1).

In the double-blind phase, total sleep time was markedly increased to a statistically highly significant degree ($P < 0.05$) by mean 90 min. Midazolam and Vesparax were equally effective with regard to increasing sleep duration. During the withdrawal phase, total sleep time decreased again to the baseline level (Figure 3).

Awakenings

During the first placebo phase, all patients awoke at least once and around 40% awoke more than twice (Figure 1). During treatment with both active medications, there was a substantial decrease in the number of awakenings ($P < 0.05$). Four of five patients slept without interruption (Figure 4).

Sleep quality

With one exception, all patients described their sleep during the first placebo phase as disturbed, whereas the patients rated it pleasant ('peaceful') on 86% of the nights during the double-blind phase. Almost half the patients complained of unpleasant dreams during the first placebo period. During both Vesparax and midazolam treatment, unpleasant dreams disappeared almost completely.

State on awakening, side-effects

From the clinical point of view, the most notable difference between the two active drugs lay in

Figure 3 Total sleep time (mean $\pm$ SD): evolution during study.

Figure 4 Percentage of patients without nocturnal awakenings: evolution during study.

patients' condition on awaking on the mornings following drug intake. After 95% of the midazolam nights the patients awoke feeling rested and refreshed with no signs of hangover or of feeling 'drugged'. In contrast, after 19% of the Vesparax nights, patients complained of tiredness on awakening and four times (5%) drowsiness was reported (Figure 5). There was no mention of side-effects by patients in the midazolam group whereas side-effects (hangover) were reported five times in the Vesparax group. The dosage had to be reduced for this reason in one case.

Patients' subjective assessment

According to the subjective assessment, patients were satisfied with the effect of midazolam on 96% of the nights. The corresponding figure for Vesparax

Figure 5 Patients' state on awakening, averaged over the 5 nights of the verum phase. Whereas in the midazolam group, 5% of the patients reported tiredness on awakening, the corresponding figure for the Vesparax group was 19%, with an additional 5% reporting side-effects (drowsiness).

was 83%. During both placebo phases, patients described the sleep quality as unsatisfactory (Figure 6). The patients' overall assessment is in agreement with the therapeutic index calculated for each of the two treatments.

Figure 6 General assessment by patients made each morning following Vesparax or midazolam administration.

Therapeutic index

In total, amongst patients receiving midazolam, sleep onset occurred within 20 min on 60 nights and there were four reports of tiredness on the following morning. Thus, the Q_{TI} calculated on this basis (60:4) is 15. Amongst patients receiving Vesparax, sleep onset occurred within 20 min 52 times and there were 18 complaints of tiredness, drowsiness or hangover on awakening. The Q_{TI} thus obtained (52:18) is 2.9. The comparison of the therapeutic indices demonstrates that clearly more patients of the midazolam group fell asleep quickly and awoke refreshed and without hangover or side-effects ($P < 0.05$) than in the Vesparax group.

Laboratory findings and interactions

There were no pathological alterations in either the midazolam or the Vesparax group. No interactions with co-medication were observed in either group.

Discussion

This study comparing the efficacy and safety of midazolam

(15 mg) and of Vesparax in patients with differing degrees of insomnia demonstrated that both treatments are effective compared with placebo. Both bring about a highly significant reduction in sleep onset latency and in the number of awakenings, an increase in total sleep time and an improvement in the sleep quality. In the midazolam group, patients more frequently fell asleep within 20 min than in the Vesparax group. This result is in agreement with the findings of other clinical studies in which midazolam has been shown to have a more rapid onset of action than the reference compounds.

Vesparax is known to be a particularly effective agent for the maintenance of sleep, i.e. for use in insomnias typified by troubled and disturbed sleep with awakenings. However, midazolam—a compound characterized by a very short duration of action—was also able to increase sleep duration and reduce the number of awakenings equally as effectively as did Vesparax. It would thus appear that many patients, having fallen asleep easily are able to continue to sleep deeply and without interruption, even after the direct pharmacological effect has disappeared.

However, for us, the most decisive difference between the two products lay in the state on morning awakening. After midazolam, the patients almost without exception reported feeling refreshed and rested on awakening. In contrast, patients who had received Vesparax complained of tiredness and drowsiness, a finding which is consistent with reports by other authors describing hangover after administration of secobarbital (Bond & Lader, 1972; Borland & Nicholson, 1975; Porvin *et al.*, 1975; Saario & Linnoila, 1976; Hink *et al.*, 1978).

In our study, we used a fixed dosage schedule: as is usual with hypnotics, each patient received one tablet at night. Reduction of the Vesparax dose by one half-tablet would probably reduce the frequency of hangover and drowsiness on the following morning but would also probably delay the onset of action and reduce the intensity of effect. Therefore, lowering the Vesparax dose would be unlikely to improve the therapeutic index to any marked degree.

On the basis of our findings in this study, we conclude that midazolam is equally as effective as Vesparax in treating sleep disorders of different origin and degree, that midazolam is better tolerated, and that it has no residual 'hangover' effect. Thus, when one also takes into consideration the risks of treatment with a barbiturate combination, preference must be given to the better tolerated and equally effective compound midazolam.

References

- BOND, A.J. & LADER, M.H. (1972). Residual effects of hypnotics. *Psychopharmacologia*, **25**, 117–132.
- BORLAND, R.G. & NICHOLSON, A.N. (1975). Comparison of the residual effects of two benzodiazepines (nitrazepam and flurazepam hydrochloride) and pentobarbitone sodium on human performance. *Br. J. clin. Pharmacol.*, **2**, 9–17.
- FELDMIEIER, CH. & KAPP, W. (1983). Comparative clinical studies with midazolam, oxazepam and placebo. *Br. J. clin. Pharmacol.*, **16**, 151S–155S.
- HELCL, I., LUPOLOVER, R., BUCH, J.-P. & AMREIN, R. (1981). Evaluation of the efficacy and tolerance of orally administered midazolam as hypnotic agent compared with oxazepam in the treatment of mild to moderate insomnia. *Arzneimittel.-Forsch.*, **31**, 2284–2287.
- HINK, R.F., FENTON, W.H. Jr, TINKLENBERG, J.R., PFEFFERBAUM, A. & KOPELL, B.S. (1978). Vigilance and human attention under conditions of methylphenidate and secobarbital intoxication: an assessment using brain potentials. *Psychophysiology*, **15**, 116–125.
- LUPOLOVER, R. & BUCH, J.-P. (1981). Evaluation of efficacy and safety of midazolam administered orally in sleep disorders. *Arzneimittel.-Forsch.*, **31**, 2281–2283.
- NICHOLSON, A.N. & STONE, B.M. (1983). Midazolam: sleep and performance studies in middle age. *Br. J. clin. Pharmacol.*, **16**, 115S–119S.
- PORVIN, A.R., SALAMY, J.G., CROSIER, W.G., JONES, K.W. & DOERR, J.A. (1975). Effects of secobarbital on performance upon arousal from stage 4 sleep. *Appl. Neurophysiol.*, **38**, 240–250.
- SAARIO, I. & LINNOILA, M. (1976). Effects of subacute treatment with hypnotics, alone or in combination with alcohol, on psychomotor skills related to driving. *Acta Pharmacol. Toxicol.*, **38**, 382–392.
- SCOLLO-LAVIZZARI, G. (1983). Hypnotic efficacy and clinical safety of midazolam in shift-workers. *Br. J. clin. Pharmacol.*, **16**, 73S–78S.
- VOGEL, G.W. & VOGEL, F. (1983). Effect of midazolam on sleep of insomniacs. *Br. J. clin. Pharmacol.*, **16**, 103S–108S.