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COMPARATIVE CLINICAL STUDIES WITH MIDAZOLAM, OXAZEPAM AND PLACEBO

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1 The efficacy and safety of midazolam compared with oxazepam and placebo were investigated in 50 hospital patients (19 males, 31 females; age range 21 to 74 years) in a double-blind parallel group study.

2 On the first 2 nights (selection phase), patients received only placebo. On the next 5 nights, they received either 15 mg midazolam, 15 mg oxazepam or placebo. They received no medication on the last 2 nights and were kept under observation (withdrawal phase).

3 Compared with placebo, both benzodiazepines shortened sleep onset latency, reduced the number of awakenings and improved sleep quality. All 3 compounds were well tolerated with only few, mild side-effects (headache, nausea) in the 2 verum groups. Psychometric performance was not impaired on the morning following drug administration. The overall patients' assessments showed 80% satisfaction with midazolam, 66% with oxazepam and 10% with placebo.

4 Midazolam and oxazepam yielded similar results, although midazolam induced sleep more rapidly and was rated more favourably by the patients.

5 Midazolam, in a dose of 15 mg, is thus an effective, fast-acting, well-tolerated hypnotic without residual effects and is suitable for the treatment of insomnia of mild to moderate degree. Oxazepam in a dose of 15 mg is also well suited for the treatment of sleep disorders, particularly if a rapid onset of action is not required.

Introduction

The new benzodiazepine derivative, midazolam, possesses a short pharmacological duration of action, an elimination half-life of 1.2–2.3 h and no active metabolites with any significant effect on the duration of action (Amrein *et al.*, 1981; Heizmann *et al.*, 1983). Oxazepam is frequently used in a dose of 15 mg as a hypnotic in several countries. In this dose, it does not result in any residual impairment of performance on the following day (Nicholson, 1979). Midazolam was investigated in a hospital setting to assess its efficacy and tolerability in the treatment of insomnia, and to determine whether its theoretically promising pharmacokinetic properties and behaviour can be confirmed as clinically useful in man in terms of quick onset of action and avoidance of hangover or of impairment of patients' state on awakening.

Methods

Patients

The study population was selected from hospitalized male and female patients who complained of difficulties connected with sleeping. Female patients of childbearing potential were not admitted unless they were using a reliable contraceptive method. Further patient categories to be excluded were patients in poor general health with decompensated disease of the parenchymatous organs, those with known hypersensitivity to benzodiazepines, with severe psychoses or psychoneuroses, with severe chronic pain and patients taking other psychotropic substances with a sedative component. The patients were informed of the objective and modalities of the study in accordance with the Declaration of Helsinki and their consent to participation obtained.

Dosage and study procedure

On nights 1 and 2 all patients received a brightly coloured placebo. Only patients who still complained of difficulties in sleeping during this selection phase were accepted into the following double-blind phase. This second phase lasted five nights (i.e. nights 3 to 7); patients were divided at random into 3 parallel

groups and received either 15 mg midazolam, 15 mg oxazepam or placebo in the form of tablets of identical appearance. On the last 2 nights (withdrawal phase), patients received no medication but were kept under observation.

Parameters measured and tests conducted

The following parameters were estimated: sleep onset latency and sleep duration (periodically checked by nursing staff); number of nocturnal awakenings, dreams, state on awakening, side-effects and patients' overall assessment (assessed by patients themselves); subjective assessment by medical staff, efficacy and safety. In addition, simple psychometric testing (HAWIE 3, memory test, Grünberger test) was carried out on the mornings after administration of the compounds in order to assess more objectively patients' state on awakening.

Results

Patient population

Fifty hospitalized patients with an age range of 21–72 years were studied; in the double-blind phase, 19 received midazolam (seven males and 12 females; age 33 ± 13 years), 15 received oxazepam (four males and 11 females; age 34 ± 13 years) and 16 received placebo (eight males and eight females; age 27 ± 5 years).

Sleep onset latency

The most frequent type of insomnia in the studied population was a difficulty in falling asleep. On the second night of the selection phase, no patient fell asleep within 20 min and only four of 50 patients (8%) had fallen asleep within 40 min. During the ensuing double-blind phase, there was a statistically significant inter-group difference (Kruskal-Wallis test $\alpha = 0.0002$). In the placebo group, sleep latency remained equally as unsatisfactory as in the selection phase. In the two verum groups, however, sleep onset was significantly more rapid than that in the placebo group (Mann-Whitney test $\alpha < 0.05$). The most favourable results were obtained with midazolam: in the mean for all nights, 30% of the patients fell asleep in less than 20 min and a further 54% were asleep in 20–40 min. In the placebo group, no patients fell asleep within 20 min and only 29% were asleep within 40 min, i.e. 71% awaited sleep for over 40 min. The results of the oxazepam group lay between those of the placebo and midazolam groups: fewer patients than in the midazolam group (16%) fell asleep within 20 min but the number falling asleep in 20–40 min was greater (57%) than in the placebo group (Figure 1).

In the withdrawal phase, the values for all three groups returned almost to baseline levels, i.e. the drug or placebo effects disappeared without any sign of rebound insomnia.

Sleep duration

During the selection phase, mean sleep duration was 6.5 h, i.e. normal for this age-group and, in the treatment phase, increased to a mean of 7 h 10 min in the midazolam group and 7 h 20 min in the oxazepam group. There was no statistically significant inter-group difference in either the double-blind or the withdrawal phase. Clinically, this is of no relevance as, in this patient group, total sleep duration, even as assessed by the patients themselves, was not too short. (Figure 2).

Nocturnal awakenings

The second most frequent type of insomnia in our

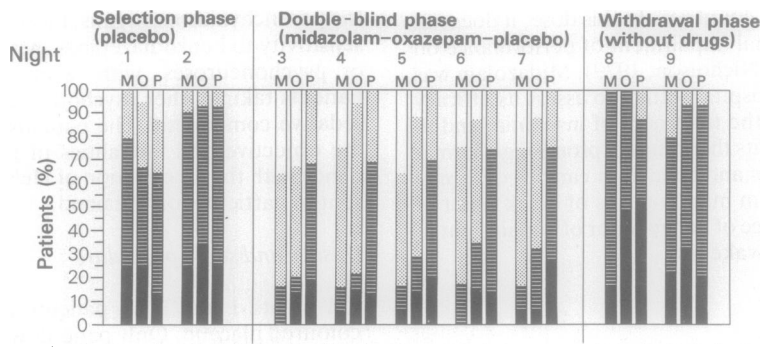

Figure 1 Sleep onset latency. It can be seen that, in the double-blind phase, midazolam and oxazepam significantly reduce sleep onset latency in comparison with baseline and the reference placebo group. In the withdrawal phase, there was a tendency to return to baseline with no sign of rebound insomnia. □, 20 min; ▨, 20–40 min; ▤, 40–60 min; ■, not in 1 h.

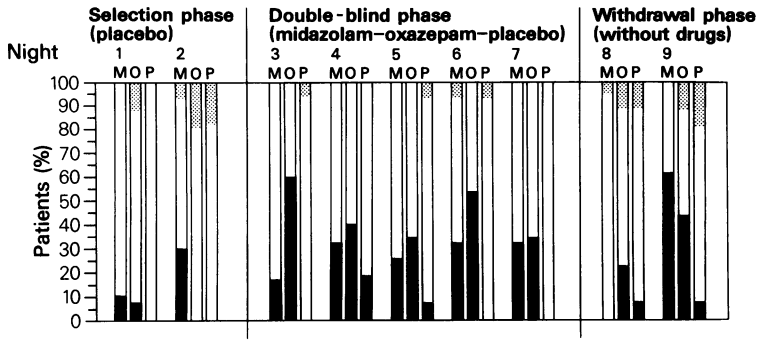

Figure 2 Total sleep duration (in hours). There was a slight, non-significant increase in all 3 groups in the double-blind phase, patients in the verum groups sleeping somewhat longer than those receiving placebo. There is a gradual tapering off of effect in the withdrawal phase. ▩, 5 h; □, 6–7 h; □, 8–10 h.

patients was disturbed sleep with awakenings. There was no inter-group difference in this regard in the selection phase (Figure 3). However, during the double-blind phase, in contrast to placebo, midazolam and oxazepam reduced the number of awakenings ($P < 0.0001$). With midazolam, exactly two-thirds of the nights were completely uninterrupted and, on almost one-third of the nights, there were one to two awakenings. In the oxazepam group, on 55% of the nights, patients slept without interruption, on 35% there were one to two awakenings and on 10% there were more than two awakenings. In the placebo group, only 13% of the nights were undisturbed, 69% featured one or two awakenings, and 18% had more than two awakenings (Figure 3).

There was a return to the values of the selection phase after treatment was withdrawn. Thus, for this parameter, there was again no sign of rebound phenomena.

Dreams

For midazolam and oxazepam in the majority of cases, no dreams were registered. Unpleasant dreams were rare and no nightmares were experienced with midazolam.

Sleep quality

The sleep quality was markedly improved with both active drugs. In the selection phase, 53% of the placebo group, 40% of the oxazepam group and 34% of the midazolam group described their sleep as peaceful. During the verum phase, the corresponding figures were 86% (+52%), 78% (+40%) and 59% (unchanged) in the midazolam, oxazepam and placebo groups, respectively (Figure 4).

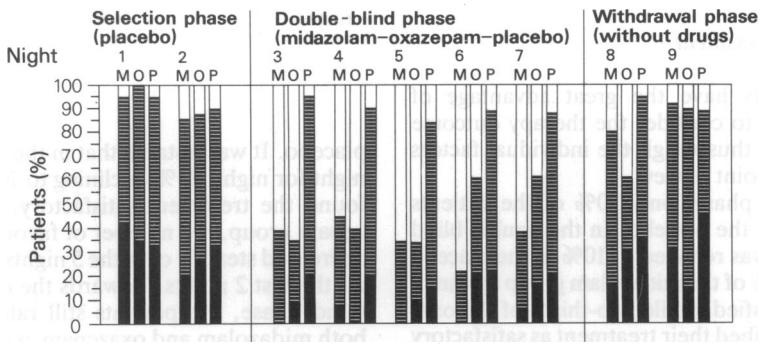

Figure 3 Number of awakenings. Midazolam and oxazepam markedly decreased the number of awakenings compared with placebo ($P < 0.0001$), the more favourable results being shown with midazolam. Again, there are no signs of rebound phenomena in the withdrawal phase. □, None; ▤, once–twice; ■, more than twice.

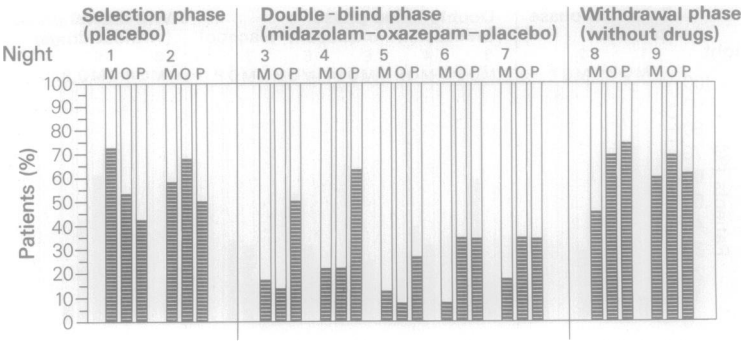

Figure 4 Sleep quality. The 2 benzodiazepines markedly improved sleep quality but this remained unchanged in the placebo group. □, Peaceful; ▤, disturbed.

Safety

The safety of all 3 preparations was described by the physician as 'very good' for all patients. Complaints were rare in all three groups. Those that were—rarely—reported (headache, slight nausea) in the two verum groups were mild in degree and in no case necessitated treatment withdrawal.

Psychometric tests

Statistically significant differences amongst the three groups were seen in the baseline values (Kruskal-Wallis test $P < 0.1$). In an attempt to balance out these differences at least partially, we studied not the absolute measured values but rather the difference from baseline. In this analysis, none of the tests revealed a significant difference in comparison with baseline. Thus, neither of the two benzodiazepines was shown by our testing procedures to impair patients' psychometric performance on the morning after administration of the hypnotic.

Patients' overall assessment

Global assessments have the great advantage of making it possible to consider the therapy outcome 'in the round' and thus weigh the individual factors from a subjective point of view.

In the selection phase, only 20% of the patients were satisfied with the placebo. In the double-blind phase, this figure was reduced to 10% in the placebo group. Almost 80% of the midazolam group (mean of 5 nights) were satisfied, while two-thirds of the oxazepam group described their treatment as satisfactory (Figure 5).

The results for midazolam and oxazepam are better to a highly significant degree ($P < 0.01$) than with placebo. It was notable that in the midazolam group, night for night, 85% declining to 70% of the patients found the treatment satisfactory, while in the oxazepam group, the number of favourable assessments decreased steadily over the 5 nights from 80% to 53% on the last 2 nights. Towards the end of the double-blind phase, the patients still rated the efficacy of both midazolam and oxazepam as significantly better than placebo ($P < 0.01$), although the efficacy of midazolam received a significantly more favourable ($P < 0.05$) assessment than that of oxazepam.

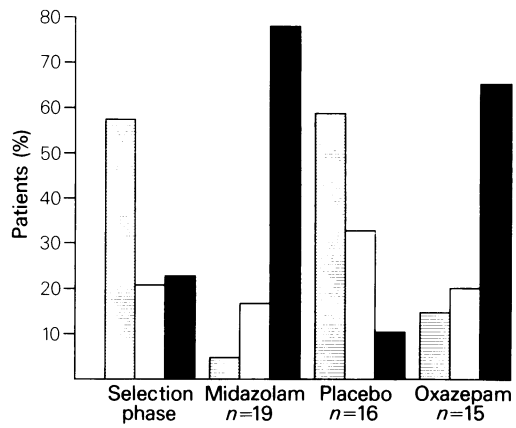

Figure 5 Patients' overall assessment. Midazolam was significantly more favourably rated than placebo ($P < 0.01$), and this rating remained consistently high for all 5 days of the double-blind phase, whereas the oxazepam rating (initially quite high) declined over this period. ■, Satisfactory; □, partially satisfactory; ▤, unsatisfactory.

Discussion

Our study was conducted in 50 patients in a surgical clinic who were suffering from placebo-resistant insomnia in which pain was not an important component. The insomnia was expressed mainly in difficulty in falling asleep and frequent nocturnal awakening which had relatively little influence on the sleep duration as a whole. This type of sleeping difficulty may be regarded as typical for subjects in a hospital setting as, apart from the relatively early 'lights out' which in itself makes falling asleep difficult, the patient is subject to worry and apprehension, and has to come to terms with the unfamiliar surroundings.

Furthermore, extraneous disturbances are more frequent than at home and thus the patient is more likely to be awoken in the night.

With regard to efficacy, our study demonstrated marked differences between placebo and the two active compounds oxazepam and midazolam. The sleep onset latency was shortened by both benzodiazepines to a highly significant degree and the number of awakenings was also reduced. According to the patients' subjective assessment, sleep quality was substantially improved by the two active drugs, but not by placebo. All three compounds were well tolerated.

There were also some differences between the two benzodiazepines. The patients reported a faster onset of action for midazolam, although results for the other sleep parameters were very similar. These results may find their explanation in the fact that oxazepam is less rapidly absorbed than midazolam. Of the patients receiving midazolam, 78% declared themselves completely satisfied with the treatment and a further 7% rated the midazolam treatment as partially satisfactory. In contrast, only 10% of the patients of the placebo group felt satisfied with the treatment. The results for oxazepam lay between these two extremes but were closer to those for midazolam. A surprising finding was the constancy of the favourable patient rating of midazolam as against the marked decline in the number of favourable ratings for oxazepam during the 5 days of administration. At the end of the double-blind phase, this difference was significantly in favour of midazolam. The reason for this change in assessment has not been determined.

It was reassuring to find that performance, as assessed by simple psychometric tests, not using testing apparatus, was not impaired in the morning after drug intake. This also corresponds to the subjective experience of the patients who reported no hangover or other undesirable after-effects.

On the basis of both objective medical observations and patients' assessment, we thus conclude that midazolam, in a dose of 15 mg, is an effective hypnotic without side-effects that is suitable for the treatment of insomnia of moderate to severe degree and which induces sleep more rapidly than oxazepam.

This double-blind study shows that statistically significant differences can be demonstrated between placebo and the two active compounds. Midazolam and oxazepam yielded comparable results, although midazolam induces sleep more rapidly and was more favourably assessed by the patients.

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