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ORIGINAL PAPER

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Treatment of primary insomnia with trimipramine: an alternative to benzodiazepine hypnotics?

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Summary A group of 19 middle aged patients suffering from primary insomnia according to the DSM-III-R were treated in a single-blind study with trimipramine, a sedating antidepressant. A total of 15 patients completed the study protocol and were evaluated. The present pilot study aimed at investigating the sleep-inducing properties of trimipramine, and at clarifying the question of whether short- or long-term rebound insomnia occurs after discontinuation of this drug. At four measurement points, i.e. under baseline conditions, under treatment and 4 and 14 days after drug discontinuation, sleep was recorded with an ambulatory-electroencephalogram (EEG) monitoring device in the patient's home environment. Simultaneously, psychometric tests were applied to measure withdrawal symptoms, subjective sleep quality and well-being during daytime. Trimipramine at a mean dose of 166 ± 48 mg led to a significant increase in sleep efficiency, total sleep time, and stage 2% sleep-period time (SPT), whereas a significant decrease in wake time and stage 1% SPT was noted. Insomniac patients reported an improvement in subjectively perceived sleep quality following trimipramine. Additionally, an improvement in well-being during the daytime occurred. Negative side effects were limited to dry mouth due to the anticholinergic properties of the drug. Discontinuation of trimipramine did not provoke either short- or long-term rebound insomnia in objective and subjective sleep measurements considering mean values of the whole sample, although a subgroup of patients did display total sleep times below baseline values during short- and long-term withdrawal, but generally without a concomitant worsening of sleep quality according to the sleep questionnaire.

Key words Insomnia · Trimipramine · Rebound insomnia · Hypnotic withdrawal

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Introduction

Benzodiazepines are presently the hypnotics most frequently used in the treatment of insomnia (Woods et al. 1987; Lohse and Müller-Oerlinghausen 1992; Hohagen et al. 1993). However, as knowledge of the total efficacy/side-effect spectrum of benzodiazepines has grown in recent years the uncritical attitude towards this class of compounds has undergone major changes. Aside from the possible development of tolerance and the potential for addiction (Tryer 1988) the main problem is the risk of rebound insomnia, which can endure for several weeks after withdrawal of the drug (Kales et al. 1983; Gillin et al. 1989; Kales et al. 1977). Epidemiological data indicate that one of the main causes for chronic use of benzodiazepine hypnotics may be that the patient tries to avoid the occurrence of rebound insomnia after discontinuation of hypnotics (Hohagen et al. 1993). Furthermore, the long-term efficacy of benzodiazepines in the treatment of chronic insomnia has not yet been proven (Consensus Conference 1984). On the contrary, a longitudinal study in general practice provided data indicating that long-term medication with benzodiazepines is of little benefit concerning chronic insomnia (Hohagen et al. 1993).

These shortcomings of benzodiazepine hypnotics stimulate studies in the field of alternative sleep-promoting substances (Hohagen and Berger 1990). Antidepressants with sedative properties are considered one of the major candidates (Ware 1983). They are considered the drugs of choice in depressed patients suffering from secondary insomnia (Ware et al. 1989; Wiegand et al. 1986). Keeping in mind the high comorbidity of insomnia with psychiatric disorders, especially depression (Hohagen et al. 1993; Ford and Kamerow 1989; Angst et al. 1989; Weyerer and Dilling 1991), the relevance of sedating antidepressants for the treatment of insomnia is already obvious. Their sleep-promoting properties and the fact that up to now dependency has not been noted with antidepressants suggest that these drugs also may be suitable for the long-term treatment of patients suffering from chronic primary insomnia. In clini-

cal practice the administration of sedating antidepressants for primary insomnia is increasing (Wysowski and Baum 1991). Controlled studies on their efficacy in the treatment of primary insomnia are, however, still insufficient. There is also the unanswered question of whether discontinuation of antidepressants is accompanied by rebound insomnia.

The aim of the present single-blind pilot study was to investigate whether trimipramine, a drug with proven antidepressive (Gastpar 1989; Lapierre 1989) and sleep promoting effects in depressed (Ware et al. 1989; Wiegand et al. 1986; Feuillade et al. 1992) and healthy subjects (Feuillade et al. 1992), is effective in the treatment of sleep disorders in patients with primary insomnia, and to evaluate whether withdrawal of the compound is accompanied by rebound insomnia. Trimipramine shows characteristics atypical of other antidepressants. Radioligand binding techniques have shown trimipramine to possess a binding potency for the D2-receptor, and a high affinity for the α 1- and H1-receptors, an effect which likely causes sedation (Richelson and Nelson 1984a, b; Peroutka and Snyder 1990). A recent study has shown a high affinity of trimipramine for the HT2-receptor, which may be relevant to the sleep-inducing properties of the drug (Gross et al. 1991). To exclude the artificial atmosphere of a sleep laboratory sleep registration was carried out by means of an ambulatory sleep-electroencephalogram (EEG) monitoring device in the patient's home environment, thus investigating the effect of trimipramine under conditions as natural as possible.

Patients and methods

A group of 19 patients suffering from primary insomnia according to the DSM-III-R (American Psychiatric Association 1987) entered the study. A psychiatric disorder was excluded (according to the DSM-III-R) in a semistructured clinical interview by two experienced psychiatrists. A thorough physical examination, computertomography of the brain (CCT), EEG, ECG and routine blood tests were required to exclude a somatic disorder.

A total of 4 patients did not complete the whole study protocol. One discontinued on day 4 of the study because of unpleasant side effects (gastric pain) under 50 mg trimipramine. Three patients dropped out on day 17 under 100 mg, day 21 under 200 mg and day 28 under 100 mg, respectively, complaining of a lack of efficacy of the treatment. The 15 patients who finished the whole study are included in the data analysis (8 males and 7 females; mean age ± SD: 49.4 ± 9.1 years). They suffered from insomnia for 9.0 ± 4.6 years.

Prescribed benzodiazepine hypnotics were being taken by 6 of these patients upon entry into the study: 1 patient had taken chlordiazepoxide (10 mg) and lorazepam (0.5 mg) for 2 months, 1 had taken oxazepam (10 mg) for 3 years, 1 had taken diazepam (5 mg) for 5 years, and 1 had taken flurazepam (30 mg) for 2 years. Another 2 patients reported using various benzodiazepines for several years, but could not remember the exact duration of hypnotic use or the name of the drug. All patients had taken the benzodiazepine hypnotics discontinuously interspersed with several drug-free periods. As the hypnotics were prescribed by the physician, and the patients had not increased the dose and no significant withdrawal symptoms had occurred when hypnotics were discontinued previously, none of these patients fullfilled the DSM-III-R criteria for hypnotic dependency. The remaining 9 patients who entered the study had all been drug-free for at least 3 months. Patients were informed in detail about the study procedures and gave written consent. The study was approved by the local ethics committee.

Sleep-EEG recording

Sleep was recorded and scored visually according to Rechtschaffen and Kales (Rechtschaffen and Kales 1968), EEG was recorded from positions C3-A2 and C4-A1, the electro-oculogram (EOG) was recorded horizontally and the electromyogram (EMG) was recorded submentally. Polysomnography was performed by means of an 8-channel ambulatory sleep-EEG monitoring device (Walter Electronics) in the patient's home environment. A laboratory technician went to the patient's home in the evening of the day when sleep recordings were scheduled to fix the electrodes, returning to detach them the following morning. On these days and during the whole study period patients were asked to follow their habitual sleep/wake schedules. Sleep-EEG recordings at each measurement point (see Treatment) were preceded by an adaptation night. The second night was evaluated for the following sleep parameters:

1. Sleep efficiency, ratio of total sleep time (TST) to time in bed (TIB) × 100%
2. Stages wake, 1, 2 and slow-wave sleep (SWS, stages 3 and 4 combined), and rapid eye movement sleep (REM), all expressed in minutes and percent of sleep-period time (SPT, time from sleep onset until final awakening)
3. Latencies, i.e. time from the beginning of the record to the first epoch of stage 2 (sleep-onset latency) and from sleep onset to the first epoch to the stage REM (REM latency) in minutes
4. Number of awakenings during SPT (at least one epoch of stage wake)
5. REM density for the first REM period and for the whole night (REM density is defined as the ratio of 3-s mini-epochs, including eye movements, to the total number of 3-s mini-epochs per REM period × 100%)

Treatment

Figure 1 displays the study design. Sleep-EEG recordings and psychometric tests were performed at baseline (day 0), day 28 (last night of treatment), day 33 (4 days after discontinuation of treatment under placebo) and again on day 42 (2 weeks after discontinuation of treatment under placebo). After adaptation the baseline night was registered under completely drug-free conditions in nine patients and under treatment with benzodiazepines in six. The aim of this procedure was to assess virtual sleep quality under conditions in which patients came to our sleep disorder center complaining about disturbed sleep. Drug withdrawal was standardised in the six patients who were treated with benzodiazepines. They were switched to 10 mg oxazepam for the first 3 days of the study, then oxazepam was decreased to 5 mg for 3 days and afterwards completely withdrawn.

Patients were treated with trimipramine for 28 days. After the baseline sleep-EEG recording trimipramine (25 mg) was administered. The dose was increased stepwise every 2 days by 25 mg. Those patients receiving benzodiazepines concomitantly received gradually tapered doses according to the schedule previously described. Thus, all patients were on monotherapy with trimipramine

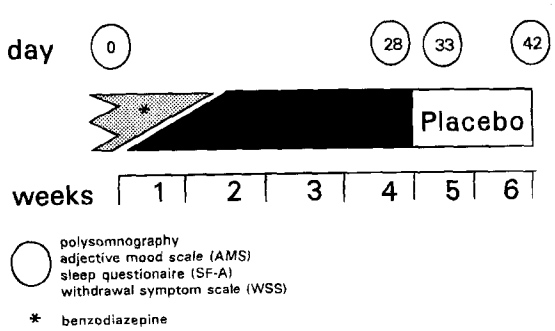

Fig. 1 Study design

6 days after inclusion in the study. Trimipramine was always administered in a single dose 1 h before "lights off".

Patients were seen once a week in our outpatient department to evaluate the clinical efficacy of trimipramine and to control side effects. The patients were blind to drug conditions, whereas the physician in charge was not, which means that patients were informed about the verum-placebo design without knowing the time when verum was switched to placebo. In the weekly consultations the drug dose was adjusted to the individual needs of each patient. Sufficient therapeutic effects was defined as a significant improvement in insomnia according to the patient's subjective perception. A 200-mg dose of trimipramine was set as the maximum dose, which could be reached in conjunction with the described tapering process after 15 days. The trimipramine requirements were as follows: 2 patients required 75 mg, 1 patient 100 mg, 3 patients 150 mg and 9 patients 200 mg. The mean highest dose of trimipramine achieved by this procedure was 166 mg ± 48 mg. After 28 days of trimipramine treatment sleep recordings were repeated to evaluate the impact of the drug on sleep-EEG variables.

Then trimipramine was discontinued in a single-blind manner. Prior to night 29 patients were administered half of the dose taken during the treatment period, substituting the other half of the dose with placebo. On the subsequent night they were switched completely to placebo to investigate whether rebound insomnia occurred after drug discontinuation. To assess short- and long-term rebound phenomena sleep-EEG was registered 4 days (day 33) and 2 weeks (day 42) after discontinuation of trimipramine. Rebound insomnia was defined as a simultaneous worsening compared to pretreatment levels of total sleep time (TST; min) in the sleep-EEG, and of subjective sleep quality in the standardised sleep questionnaire SF-A upon discontinuation of trimipramine.

Psychometric tests

All psychometric tests (apart from the side-effects check list that was filled out weekly) were applied on the same day as the sleep-EEG recordings, i.e. day 0, 28 33 and 42.

Subjective sleep quality

Subjective sleep quality was measured by means of a standardised sleep questionnaire (SF-A; Görtelmeyer 1985). The SF-A is a self-rating questionnaire that includes questions about daytime events, sleep habits, sleep quality, and the state of well-being the evening before and the morning after the investigation night. The evaluation of the 22 items yields the following five factors:
Factor 1: sleep quality (a composite score, including items like sleep latency, number and duration of nocturnal awakenings and sleep duration)
Factor 2: the feeling of being recovered in the morning
Factor 3: well-being in the evening
Factor 4: mental exhaustion in the evening
Factor 5: physical symptoms during the sleep period (i.E. myoclonus when falling asleep, precordial pain, sweating and headache during the nighttime).

Scores for each factor range from 1–5. A low score denotes the negative end of the scale (i.e. for sleep quality: very bad sleep), whereas a score of 5 represents the positive end (i.e. for sleep quality: excellent sleep).

Well-being during the daytime

To assess well-being during the daytime the Adjective Mood Scale (AMS; von Zerssen 1986) was completed. The AMS ranges from 0–56, with 0 denoting well-being, whereas a score of 56 means absolute uneasiness.

Withdrawal symptoms

Withdrawal symptoms were assessed by means of the Withdrawal Symptom Scale (WSS; Merz and Ballmer 1983). The WSS includes 20 items that focus on symptoms related to benzodiazepine or barbiturate withdrawal. All items rated from 1–4, with 1 meaning that none or only some of the time the respective symptom occurred, whereas 4 means that the symptom occurred most of the time. The values of the items are added, which yields the WSS score.

Side effects

Side effects were monitored weekly by means of a standardised symptom check list (Fischer Somatic or Undesired Effects Check List [FSUCL], Fischer-Cornelssen 1985), which includes 26 items.

Statistics

For descriptive statistics mean ± SD were calculated. For inferential statistics analyses of variance (ANOVAs; corrected according to the method of Greenhouse and Geisser) were calculated with the factor-repeated measurement (baseline, day 28, day 33 and day 42) concerning sleep variables and the results of the psychometric tests. For ANOVAs with a P value < 0.05 two-tailed t-tests for paired samples were computed to contrast the measurement points. In order to evaluate sleep-inducing properties and possible rebound effects after discontinuation of trimipramine calculation of statistical contrasts was performed in two steps: Treatment condition (day 28) was compared to baseline (day 0) and placebo (day 33 and day 42) and baseline condition (day 0) was compared to placebo (day 33 and day 42).

In a further step of the analysis the degree of treatment response and possible rebound phenomena were investigated, calculating δ values of TST in the sleep-EEG, and sleep quality in the SF-A. Delta values were calculated for treatment condition (day 28 - day 0) and placebo condition after drug discontinuation (day 33 – day 0 and day 42 – day 0). To assess age and dose effects TST under baseline and δ values of TST under treatment and placebo were correlated with age and dose of trimipramine. To investigate whether TST under baseline serves as a predictor for treatment response and possible rebound phenomena TST at day 0 was correlated with δ values of TST and sleep quality under treatment and placebo after discontinuation of trimipramine. Furthermore, TST and δ values of TST and sleep quality under treatment and after discontinuation were correlated to each other to clarify whether objective sleep recording and subjective sleep perception agree. For all correlations a Pearson correlation coefficient was used. For statistical evaluation of side effects a Cochran test was performed. For significant results contrasts were calculated according to Fleiss (1990). The level of significance for all calculations was set at 5% (two-tailed test).

Results

Under baseline conditions insomniac patients showed low sleep efficiency (78.3%), low TST (357.2 min) and high wake times (83.0 min; 12.3% SPT), whereas sleep onset time (28.8 min) for the whole group did not differ clearly from normative values of good sleepers in the correspondent age group. A closer look at the individual sleep-EEG data of every patient, however, revealed that TST showed a range from 245 min – 450 min. For further analysis of TST under baseline, during treatment and after drug discontinuation, we split up the sample into two groups, assessing a TST of 360 min as the cut-off: group I had a

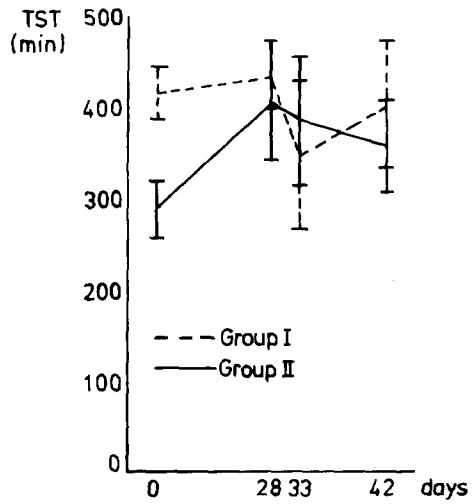

Fig. 2 Mean total sleep time (TST; min) when splitting up the sample into two groups: group I (n = 8): mean TST > 360 min; group II (n = 7): mean TST ≤ 360 min

TST > 360 min and group II had a TST < 360 min (Fig. 2). A total of 8 patients (four males and four females) displayed TST longer than 360 min (mean 417 ± 28.5 min) and 7 patients (3 females and 4 males) showed TSTs shorter than 360 min (mean 288 ± 28.6 min). There was no significant age difference between the groups (mean age 48.5 ± 9.3 years vs 50.5 ± 9.2 years). The TST was not correlated with sleep quality in the SF-A, i.e. objective sleep recording did not agree with subjective sleep perception.

To evaluate differences between patients who were drug-free (n = 9) and patients who were taking benzodiazepines at the beginning of the study (n = 6) a statistical analysis was performed to compare both groups. No significant differences could be detected between both groups during the whole study period concerning sleep-EEG recordings, psychometric tests and side effects (data not shown).

Table 1 displays the sleep variables during the four measurement points and the results of the ANOVA. (The significant results of the t-tests are given in the text). Table 2 shows mean value ± SD of the psychometric tests. Figure 3 displays TST (min), wake% SPT and subjective sleep quality (SF-A) during the whole study period.

Sleep induction

Sleep-EEG

In order to investigate sleep-inducing properties of trimipramine treatment condition (day 28) was compared with baseline condition (day 0) and placebo condition (day 33) and day 42). Regarding sleep continuity TST (min) was significantly increased under trimipramine, comparing baseline condition with treatment (difference approxi-

Table 1 Effects of trimipramine on sleep variables (mean and SD): Results of ANOVA (analysis of variance). TST total sleep time; SPT sleep period time; REM rapid eye movement; SO sleep onset; SWS slow-wave sleep; *df* degrees of freedom

	F P (df = 42.3)	Baseline	Day 28	Day 33	Day 42
Sleep continuity					
Bedtime (min)	2.43	455.3 ± 54.1	478.7 ± 48.0	426.3 ± 65.3	450.5 ± 55.7
TST (min)	3.33 *	357.2 ± 72.4	422.0 ± 53.7	366.2 ± 76.4	382.8 ± 65.4
SO latency (min)	0.56	28.8 ± 20.2	24.1 ± 26.1	21.9 ± 15.9	20.6 ± 14.8
No wake	1.52	18.1 ± 15.8	11.4 ± 10.3	12.6 ± 6.1	13.0 ± 8.2
Sleep efficiency (%)	4.37 **	78.3 ± 11.9	88.1 ± 7.4	85.5 ± 9.3	84.8 ± 8.3
Sleep architecture					
Wake (min)	2.93 *	83.0 ± 52.5	46.6 ± 31.5	57.9 ± 47.6	60.8 ± 36.6
S1 (min)	4.28 **	76.8 ± 48.8	52.8 ± 30.3	61.4 ± 39.3	50.7 ± 25.7
S2 (min)	6.23 **	192.2 ± 48.0	256.6 ± 45.0	202.9 ± 48.9	227.9 ± 47.3
SWS (min)	1.3	21.1 ± 32.6	29.2 ± 27.6	24.0 ± 27.2	28.8 ± 29.9
Wake (% SPT)	4.67 **	12.3 ± 10.7	5.3 ± 6.4	5.3 ± 4.2	8.3 ± 7.0
S1 (% SPT)	5.14 **	15.4 ± 9.1	9.6 ± 6.1	12.2 ± 7.6	10.7 ± 5.9
S2 (% SPT)	5.40 **	47.4 ± 10.6	57.5 ± 8.0	55.0 ± 8.2	54.8 ± 9.3
SWS (% SPT)	1.30	4.9 ± 7.5	6.5 ± 6.2	7.1 ± 8.6	6.5 ± 6.0
REM sleep					
REM latency (min)	0.94	100.8 ± 46.2	87.9 ± 49.4	80.2 ± 37.6	83.6 ± 42.8
REM (% SPT)	0.17	19.1 ± 7.5	20.1 ± 7.0	19.3 ± 5.6	18.9 ± 5.1
REM (min)	0.85	79.4 ± 35.1	90.1 ± 33.1	76.7 ± 32.6	79.0 ± 23.6
REM density (%)	3.80 *	16.7 ± 6.8	21.0 ± 9.7	17.3 ± 6.8	16.0 ± 5.9
REM period duration (min)	0.68	21.1 ± 12.1	18.5 ± 12.4	17.9 ± 10.3	23.0 ± 8.9
REM period density (%)	0.33	14.6 ± 10.7	15.8 ± 11.5	13.2 ± 7.0	14.8 ± 7.7

* $P < 0.05$
** $P < 0.01$

Table 2 Effects of trimipramine on psychometric tests (mean ± SD). WSS Withdrawal Symptom Scale; AMS Adjective Mood Scale; SF-A standard sleep questionnaire

	F P ($df = 42.3$)	Baseline	Day 28	Day 33	Day 42
WSS[a]	7.54 **	30.93 ± 5.70	26.13 ± 4.98	26.91 ± 5.49	26.07 ± 4.86
AMS[a]	4.40 **	22.87 ± 10.65	17.13 ± 10.68	18.79 ± 10.89	19.60 ± 12.08
SF-A[a]					
1	3.38 *	2.30 ± 0.83	3.33 ± 0.98	2.70 ± 0.96	2.77 ± 1.10
2	2.40	2.17 ± 0.63	2.98 ± 1.04	2.64 ± 0.82	2.83 ± 0.87
3	1.00	3.14 ± 0.75	3.40 ± 0.87	3.19 ± 0.70	3.35 ± 0.74
4	0.04	2.89 ± 0.84	3.00 ± 0.70	2.99 ± 0.85	2.96 ± 0.59
5	0.38	2.07 ± 0.59	1.88 ± 0.93	2.13 ± 0.65	2.11 ± 0.82

[a] For explanation see method section
* $P < 0.05$
** $P < 0.01$

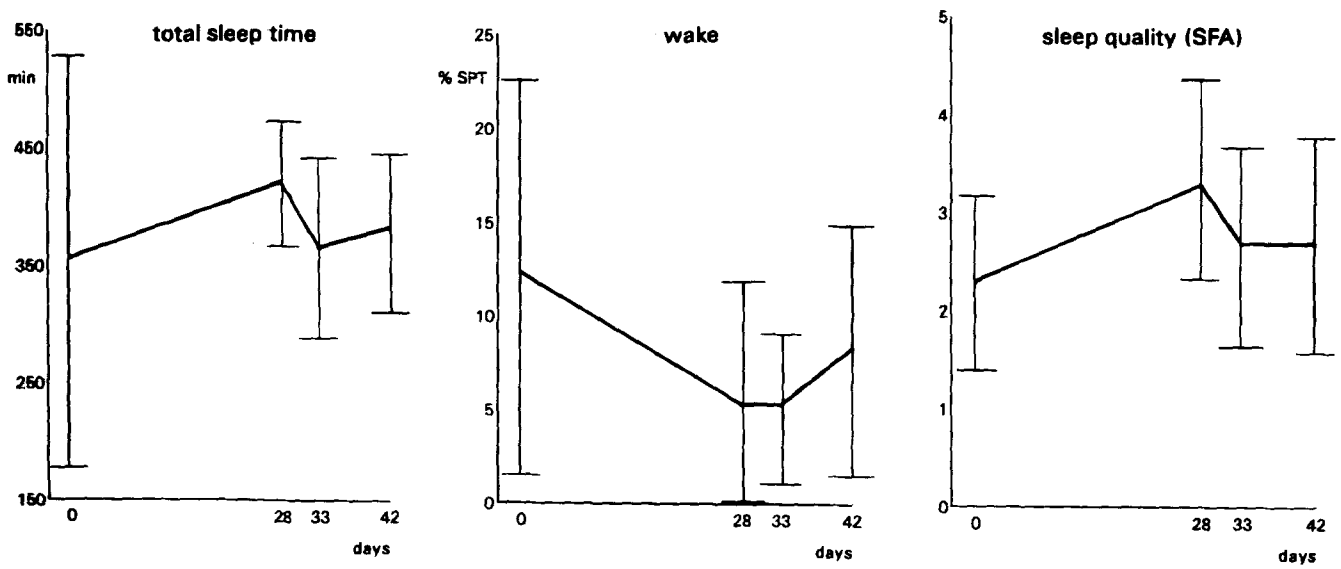

Fig. 3 TST (min), wake % sleep-period time (SPT) and subjective sleep quality (SF-A) during the whole study period (mean and SD)

mately 1 h; $P < 0.01$) and significantly decreased under placebo conditions after drug continuation to nearly the same TST (min) as before treatment ($P < 0.01$). Sleep-efficiency percent increased significantly, comparing baseline condition with treatment ($P < 0.01$), and remained significantly increased after discontinuation of trimipramine, although TST had decreased significantly after drug withdrawal. This was due to a reduction in the time spent in bed after drug discontinuation, which led to an unchanged sleep efficiency. No other changes were observed concerning sleep continuity, especially no shortening of sleep latency.

When splitting up the sample according to TST (Fig. 2) both groups showed significantly increased TSTs compared to baseline (group I: mean TST 436 ± 39.8 min; $P < 0.05$; group II: mean TST 405.6 ± 65.5 min; $P > 0.01$). At baseline TST showed a significant inverse correlation to the increase in TST under trimipramine, i.e. the lower the TST, the higher the treatment response (–0.74, $P < 0.002$). Both groups differed significantly in the dose of trimipramine administered: group I required significantly less trimipramine (mean dose 143.7 ± 54.6 mg) than group II (mean dose 192.8 ± 18.8 mg; $P < 0.05$). There was no significant correlation between increase in TST under trimipramine and age. Increase in TST correlated significantly with improvement in sleep quality according to the SF-A.

Regarding sleep architecture the administration of trimipramine (day 28) led to a significant decrease in wake ($P < 0.01$) and stage 1 sleep ($P < 0.01$), whereas stage 2 sleep increased significantly compared to baseline (day 0; $P < 0.01$). Comparing treatment (day 28) with placebo condition (day 42) stage 1 and stage 2 remained unchanged. The administration of trimipramine had no significant effect on slow-wave sleep. No significant change of REM sleep parameters was observed, other than REM density percent, which was significantly increased under trimipramine compared to baseline condition ($P < 0.05$) and placebo conditions (day 33 and day 42; $P < 0.05$).

Psychometric tests

In the standardised sleep questionnaire (SF-A) the *t*-test revealed that sleep quality (factor 1) increased significantly under treatment compared to baseline ($P < 0.01$), whereas there was a decrease in sleep quality under placebo condition after discontinuation of the drug, reaching the level of significance on day 42 ($P < 0.05$). No further changes in the SF-A were observed. There was a sig-

nificant improvement in well-being during the day, measured by the AMS under trimipramine compared to baseline ($P < 0.01$). This effect was still observed on day 33, but had vanished by day 42 (Table 2).

Rebound insomnia

In order to investigate short- or long-term rebound insomnia after drug discontinuation baseline condition (day 0) was compared with placebo condition 4 days (day 33) and 2 weeks (day 42) after trimipramine withdrawal.

Sleep-EEG

For the whole patient group there was no significant change below baseline values of TST or other sleep variables related to sleep quality after discontinuation of trimipramine on day 33 and day 42. Nevertheless, when analysing the TST of each patient a subgroup of seven patients showed decreased TSTs below baseline values on day 33. Although TST showed a tendency towards baseline values on day 42, values in four of these patients still remained lower than those at baseline.

Group I showed a trend towards a decrease of TST after discontinuation of trimipramine on day 33 (mean 350.8 ± 29.4; $P = 0.07$) and day 42 (mean 405.6 ± 70.9; n.s.) Group II still displayed signficantly improved TSTs on both placebo days (day 33. mean 383.8 ± 69.7; $P < 0.05$; day 42: mean 356.6 ± 51.2; $P < 0.05$; Fig. 2).

There was a positive correlation between TST under baseline and the decrease in TST after drug discontinuation on days 22 and 42 (–0.77; $P < 0.001$ and –0.63; $P < 0.05$, respectively). A significant correlation was also found between the increase in TST under trimipramine and the decrease in TST after drug discontinuation on both measurement days (0.75; $P < 0.001$; 0.69; $P < 0.01$). No significant correlation could be found between the decrease in TST and age, dose and subjective sleep quality in the SF-A.

Psychometric tests

Regarding the mean values for the whole group sleep quality after discontinuation of trimipramine measured by the SF-A did not fall below baseline values. Furthermore, there was no increase in withdrawal symptoms (according to the Withdrawal Symptom Scale) nor a worsening of daytime well-being (according to the Adjective Mood Scale) for the whole group (Table 2).

When analysing sleep quality in the SF-A of each patient five patients showed a worsening of sleep quality to below baseline values on day 33, and values for four of these patients were still lower than those at baseline on day 42. Two of the seven patients who showed decreased TST in the sleep-EEG fullfilled the previously adopted criteria for rebound insomnia with a concomitant worsening of sleep quality according to the sleep questionnaire SF-A on day 33, and only three did so on day 42.

Side effects

Under trimipramine significantly more patients complained about dryness of mouth ($P < 0.05$), whereas significantly fewer patients reported restlessness ($P < 0.01$). Restlessness reappeared after drug discontinuation, whereas dryness of the mouth disappeared.

Discussion

Although in clinical practice chronic insomniac patients are frequently treated with sedating antidepressants (Wysowski and Baum 1991), studies on the efficacy of antidepressants in primary insomnia are insufficient. To our knowledge this is the first study investigating the effect of an antidepressant on sleep in patients suffering from primary insomnia to have included sleep-EEG measurements. In contrast to most studies on hypnotics, sleep registration was carried out by means of the mobile long-term EEG in the patient's home environment to yield the most realistic results possible, and to exclude the artificial atmosphere of a sleep laboratory. In our single-blind pilot study we included drug-free insomniac patients and patients who, despite taking benzodiazepine hypnotics, were complaining about disturbed sleep. The reason for including both patient groups was to mimic in a naturalistic study design the situation generally encountered in clinical practice. During the whole study period there were no significant differences concerning sleep-EEG measurements, psychometric testings and side effects between the drug-free group and the patients who had previously taken benzodiazepines.

All patients fulfilled operationalised diagnostic criteria according to the DSM-III-R for primary insomnia, i.e. they complained about disturbed sleep at least three times a week with a duration of at least 4 weeks that was severe enough to cause impairment of daytime functioning and well-being. The subjective complaint about disturbed sleep was reflected in the sleep-EEG under baseline conditions by low sleep efficiency and a high wake time for the whole group, and corresponded well to sleep data on insomniac patients in the same age group from other studies recording sleep at home (Coates et al. 1982) and in the laboratory (Carscadon et al. 1976; Frankel et al. 1976). Nevertheless, the whole sample showed a wide range in TST, reaching from normal values to clearly decreased values. Thus, 8 patients complained about sleep while showing normal TSTs longer than 6 h, indicating that the underlying problem seemed to be subjective sleep-stage misperception, whereas the remaining 7 patients showed TSTs shorter than 6 h, probably due to insufficient sleep generation. Interestingly, subjective judgement of sleep quality did not correlate with objective measurement of TST in the sleep-EEG. It is well known that many insom-

niac patients consistently underestimate their amount of sleep time and overestimate the amount of time awake in comparison with laboratory data (Coates et al. 1982; Carscadon et al. 1976; Frankel et al. 1976; Killen et al. 1981).

The results of our study show that trimipramine has significant sleep-inducing properties in insomniac patients. Compared to the state before treatment the administration of trimipramine led to a significant increase in sleep efficiency, TST, i.e. patients slept approximately 1 h longer, and a significant decrease in wake time. Nevertheless, sleep latency was not shortened. As trimipramine was given 1 h before "lights off" the drug may not yet have attained central nervous activity at that time. In accordance with the literature (Ware et al. 1989; Wiegand et al. 1986) trimipramine did not suppress REM sleep and had no influence on slow-wave sleep. The sleep-inducing properties of trimipramine were reflected also in the psychometric tests. Under treatment with trimipramine patients reported a significant improvement in sleep quality on the standardised sleep questionnaire. Additionally, well-being during the daytime was improved significantly according to the Adjective Mood Scale. Thus, sleep disturbances and the daytime consequences thereof were ameliorated significantly in the objective sleep-EEG measurements and in the subjective statement of the patients on standardised questionnaires.

A significant correlation was found between TST under baseline conditions and treatment response. The lower the TST the more patients benefited from treatment with trimipramine. This was expected because patients with long TSTs can improve sleep duration only up to a certain limit ("ceiling effect"). Patients with TSTs of less than 6 h under baseline conditions needed significantly higher doses of trimipramine to achieve an improvement in their sleep problem than did patients whose TST exceeded 6 h.

Nevertheless, the high drop-out rate in our study has to be considered when evaluating the clinical efficacy of trimipramine. Of 19 patients 4 did not finish the study, 3 of whom dropped out after 17–21 days, because they did not experience an improvement in their sleep disturbance. Thus, although insomnia improved in most patients approximately every fourth patient did not benefit from treatment with trimipramine, as reflected by the drop-out rate.

One of the primary aims of this study was to investigate whether short- or long-term rebound insomnia occurred after discontinuation of trimipramine. For this purpose trimipramine was discontinued in a single-blind way relatively abruptly (within 2 days). Before discussing our data some methodological issues must be addressed. The concept of rebound insomnia has been discussed controversially. In most studies rebound insomnia is defined as a significant deterioration to below baseline levels in one or more sleep measures such as increased sleep latency, increased total wake time or wake time after sleep onset, reduced TST or reduced sleep efficiency (for overview see Gillin et al. 1989). Generally, patients' subjective perception of sleep quality is not included. However, up to now there is no widely recognised definition of rebound insomnia. In our study we defined rebound insomnia as the decrease in TST with concomitant worsening of subjective sleep quality according to the standardised sleep questionnaire. Comparing baseline with placebo condition 4 days and 2 weeks after trimipramine withdrawal, no signs of short- or long-term rebound insomnia could be detected when looking at mean values of the whole patient group. Although TST decreased significantly the values never fell below TST as measured under baseline conditions before treatment with trimipramine. Other variables of sleep continuity and sleep architecture, especially sleep efficiency and wake % SPT, remained unchanged compared to the state before treatment. Furthermore, after discontinuation of trimipramine no increase of withdrawal symptoms was reported on the withdrawal symptom scale. Although no short- or long-term rebound insomnia could be found concerning the mean values for the whole group, a closer analysis revealed that a subgroup of seven patients showed a marked worsening of TST after discontinuation of trimipramine. Nevertheless, only two of them showed a concomitant worsening of sleep quality according to the sleep questionnaire. Thus, the worsening of TST in the sleep-EEG was not reflected by the subjective perception of most patients. Further placebo-controlled studies are needed to clarify whether rebound insomnia occurs regularly after abrupt withdrawal of antidepressants. We conclude from our data that abrupt discontinuation of antidepressants should be avoided in the treatment of insomniac patients.

Longer sleep duration under baseline and smaller treatment response under trimipramine were correlated with a more pronounced decrease in TST after drug withdrawal. Thus, patients with an underlying sleep state misperception without showing evidence of shortened sleep in the sleep-EEG showed little improvement in insomnia under trimipramine and a marked worsening of TST after drug discontinuation in the sleep-EEG. On the other hand, patients with evidence of shortened sleep in the sleep-EEG showed a clear benefit from drug treatment and maintained an improved TST after discontinuation of trimipramine. This finding suggests that the sleep EEG may be a helpful instrument in selecting an adequate treatment method for insomniac patients. Patients with no signs of insomnia in the sleep-EEG may benefit more from cognitive-behaviour therapy to correct their subjective misperception of sleep, whereas patients with signs of sleep disturbance in the sleep-EEG may be candidates for pharmacological treatment. However, further research on this topic must consider that subjective perception of sleep quality very often does not correlate with the sleep-EEG measurement.

The treatment with trimipramine was well tolerated. The only remarkable side effect was dryness of the mouth, and restlessness was reported less frequently. Nevertheless, the sleep-inducing properties of trimipramine have to be carefully weighed against possible side effects of antidepressant treatment in primary insomnia. The anticholinergic properties of the drug must be considered, especially in elderly patients, and routine blood tests must be per-

formed to control for changes in blood count and liver enzymes. Furthermore, the mean dose of 166 mg necessary to improve sleep was high. In contrast to the treatment with benzodiazepine hypnotics the dose of sedating antidepressants must be increased stepwise to yield a sleep-inducing effect, and every patient requires an individual dose. On the other hand, as the development of addiction is unknown under treatment with antidepressants, these drugs seem to be especially suitable for long-term administration. Considering the advantages and disadvantages of treating primary insomniac patients with trimipramine this drug seems to be an effective alternative to benzodiazepine treatment, especially for chronic insomniac patients.

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