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Effect of a Reversible Monoamine Oxidase-A Inhibitor (Moclobemide) on Sleep of Depressed Patients

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The effect of moclobemide, a short-acting, reversible, preferential monoamine oxidase-A inhibitor in a 4-week therapeutic trial, on the sleep of ten depressed patients, was assessed by polysomnographic recordings. Compared with their time on placebo, patients receiving moclobemide showed improved sleep continuity, particularly during the intermediate and late stages of drug administration. The total increase in sleep time was comprised of larger amounts of stage 2 non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. Withdrawal of moclobemide was followed by a further increase of REM sleep, although values did not surpass those sometimes observed in adults with normal sleep. In these patients, the symptoms of depression were rated as being significantly improved during the study period.

The most predictable sleep abnormalities of endogenous depression consist of changes in wakefulness, non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep (Gold *et al*, 1988). They include: prolonged sleep latency, increased wakefulness, and early morning awakening; diminished slow wave sleep (stages 3 and 4); as well as short REM sleep latency and redistribution of REM sleep to the first half of the night (Gillin *et al*, 1984; Reynolds & Kupfer, 1987).

Many tricyclic, heterocyclic and monoamine oxidase inhibitor (MAOI) antidepressants suppress REM sleep and on discontinuation produce a significant rebound of REM sleep which can persist for many days or weeks. In some studies, onset of clinical improvement coincided with the attainment of total REM sleep suppression, which led to the suggestion that restoration of normal mood was dependent on the abolition of REM sleep (Vogel *et al*, 1980) or at least that this was a good predictor of clinical response (Dunleavy & Oswald, 1973; Passouant *et al*, 1973; Gillin *et al*, 1978; Kupfer *et al*, 1983). In contrast, trimipramine and amineptine increase REM sleep during chronic treatment (Di Perri *et al*, 1986; Wiegand *et al*, 1986).

The benzamide derivative moclobemide is a short-acting (half-life = 1 h), reversible, and selective brain monoamine oxidase-A (MAO-A) inhibitor (Da Prada *et al*, 1988). In contrast to the non-selective and irreversible MAOIs, moclobemide is devoid of hepatic toxicity, as well as having a very low liability to increase the pressor effect of dietary tyramine, so that strict diet restrictions may not be necessary (Amrein *et al*, 1988).

The aim of the present study was to determine the effects of moclobemide on sleep in patients with a depressive syndrome.

Method

Patients

Ten patients (three male, seven female), of mean age 44 ± 12 years, were included in the study. Their diagnoses (DSM-III) were: unipolar manic-depressive psychosis (six), major depressive disorder (three), and atypical depression (one).

All previous medication was withdrawn, 7–10 days prior to the study, and replaced by placebo. All patients and their relatives were informed about the objectives of the investigation, and gave their consent to participation.

Investigation

Polysomnographic sleep recordings were performed during the initial, intermediate, and late stages of treatment with moclobemide.

The period of investigation was 35 days, of which 16 were spent in the sleep laboratory. The first night was for the patient's adaptation to the laboratory; on the succeeding three nights, coinciding with the days on which placebo was taken, sleep was recorded and quantified, to estimate the extent and nature of sleep disturbance prior to treatment. On days 5–32, patients took moclobemide during the day. The initial dose was 150 mg daily, but this was then increased rapidly, so that by day 7, the maximum of 300 mg was being received, taken in three divided doses (08.00, 13.00 and 18.00 hours). The 300 mg dose was maintained from day 5 until day 32, so that patients received moclobemide for 28 days. During the investigation, patients came to the laboratory for nights 5–7 (initial stage of treatment), 18–20 (intermediate stage), and 30–32 (late stage). On the intervening nights, they slept at home. On the three days (33–35) following cessation of treatment, the patients received placebo, so that the effects of withdrawal of moclobemide on sleep could be observed.

Patients were interviewed by the psychiatrist during the first day of the baseline period, on treatment days 3, 7, 14, 21 and

28, and during the last day of the withdrawal period. The clinical consultation included administration of the Hamilton Rating Scale for Depression (HRSD) and Beck rating scale, as well as a self-evaluated rating scale.

On the nights when the patients attended the sleep laboratory, polygraphic sleep recordings were carried out over 8 h, using frontal, parietal, and occipital EEG leads, right and left electro-oculograms, chin electromyogram, ECG, and impedance thoracic electroplethysmography.

The sleep records were coded and scored blind. The variables scored were as follows:

(a) onset latency for NREM sleep (NREM sleep, from lights out to the appearance of the first spindle);
(b) total time awake;
(c) time awake after the onset of sleep;
(d) number of awakenings;
(e) total duration of sleep and duration of stages 1, 2, 3, and 4 NREM sleep;
(f) duration of REM sleep in minutes and as a percentage of total sleep time;
(g) REM latency (from the first spindle to REM sleep onset).

Data analysis

The mean value of each variable for placebo baseline, initial, intermediate, and late drug administration, and placebo withdrawal nights was tested for significance, using a one-way ANOVA, followed by comparison with placebo using the Scheffé test. The Kruskal-Wallis ANOVA by ranks was used to test whether any of the following were related to treatment: scores for clinical impression of severity of depression, HRSD and Beck rating scale, self-evaluation rating scale, or blood pressure fluctuations. When appropriate, the statistical significance of differences was assessed by the Wilcoxon matched pairs test.

Effect of moclobemide on sleep variables

Sleep was disturbed in all patients prior to treatment. During the placebo baseline period, latency to NREMS averaged 84.2 min, while in the period of moclobemide administration, there was a non-significant reduction of this value to a mean of 48.3 min. Total baseline time awake was 192.4 min, while time awake after the onset of sleep was 116.4 min — both of which were significantly reduced during moclobemide administration and in the withdrawal phase (Figs 1 and 2). These were accompanied by an increase in total sleep time (Fig. 3) from an average of 287.6 min during baseline to a mean of 345.2 min during the drug administration period.

During moclobemide administration, a significant increase in total NREM sleep was observed, which was maintained in the withdrawal period (Fig. 4); this was coupled with an increase in stage 2 (Fig. 5). With regard to slow wave sleep, stage 3 lasted only 2.2 min during the baseline period, and there was a slight, non-significant increase in this stage when patients were given moclobemide. Stage 4 was almost totally absent throughout the whole study period.

During the baseline period, the mean duration of REM sleep was 52.6 min (16.4% of total sleep time). On administration of moclobemide, REM sleep underwent a progressive increase,

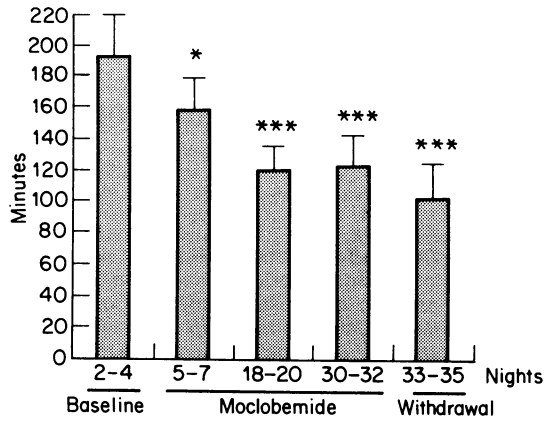

FIG. 1 Total wake time. $*P<0.05$; $***P<0.001$.

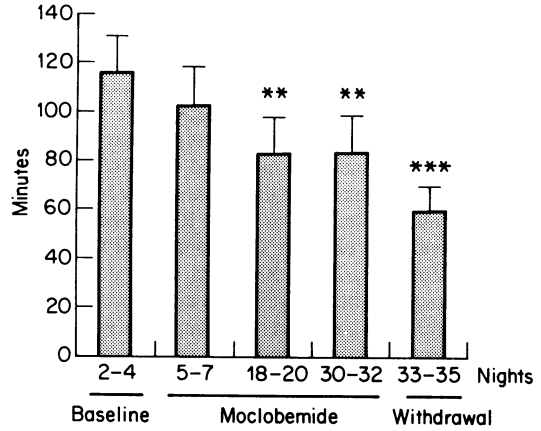

FIG. 2 Wake time after sleep onset. $**P<0.01$; $***P<0.001$.

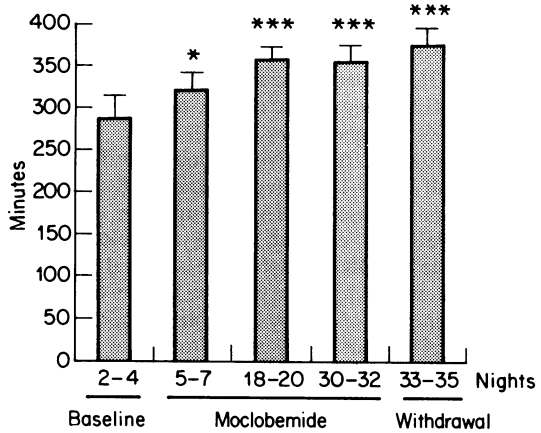

FIG. 3 Total duration of sleep. $*P<0.05$; $***P<0.001$.

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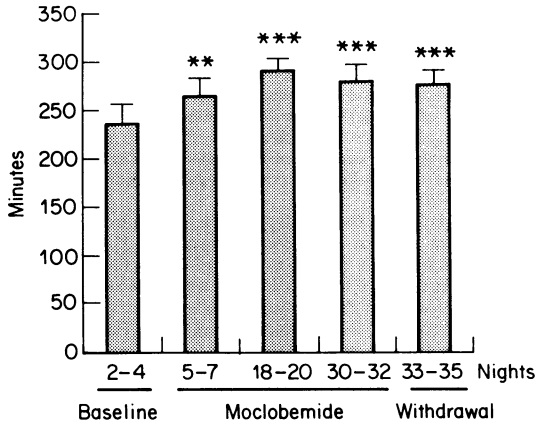

FIG. 4 NREM sleep time. $^{**}P < 0.01$; $^{***}P < 0.001$.

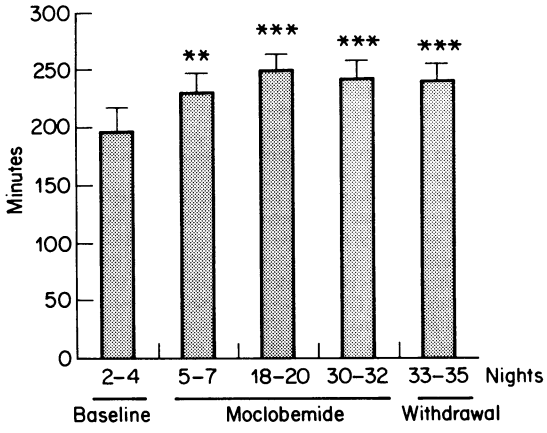

FIG. 5 Stage 2 non-REM sleep. $^{**}P < 0.01$; $^{***}P < 0.001$.

which became significant during the intermediate and late stages. During withdrawal, there was a further increase of REM sleep both in minutes and as a proportion of total sleep time, although the values did not surpass those observed in some adults with normal sleep (Figs 6 and 7). At baseline, mean REM sleep latency was 102.3 min; in five of the ten patients, the latency of the first REM period was short compared with healthy adult subjects, i.e. between 28 and 71 min. During moclobemide administration REM sleep latency was significantly increased, and significantly decreased on moclobemide withdrawal (Fig. 8).

Antidepressant effect

The efficacy of treatment was assessed by clinical impression as — very good in two patients, good in four, and moderate in four. Moclobemide was very well tolerated in eight patients, well in one and moderately well in one, patient each. The

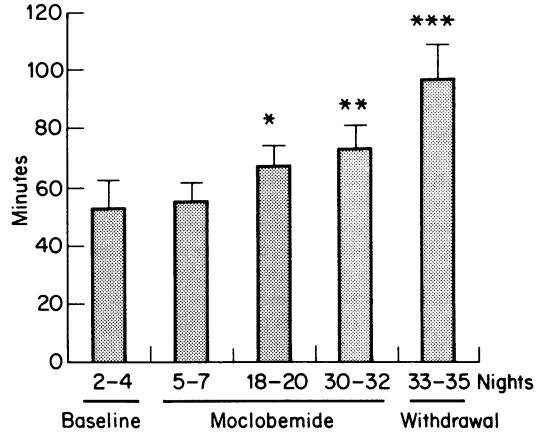

FIG. 6 REM sleep time in min. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

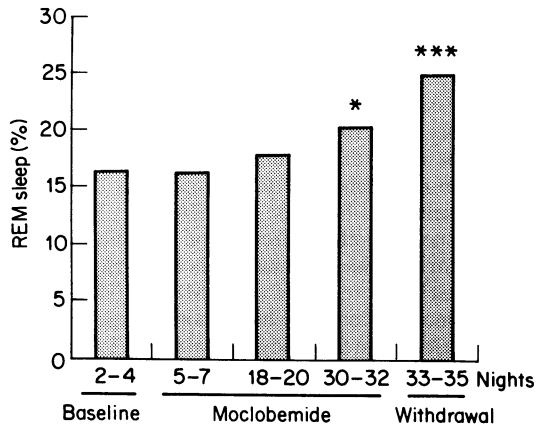

FIG. 7 REM sleep as percentage of total sleep time. $^{*}P < 0.05$; $^{***}P < 0.001$

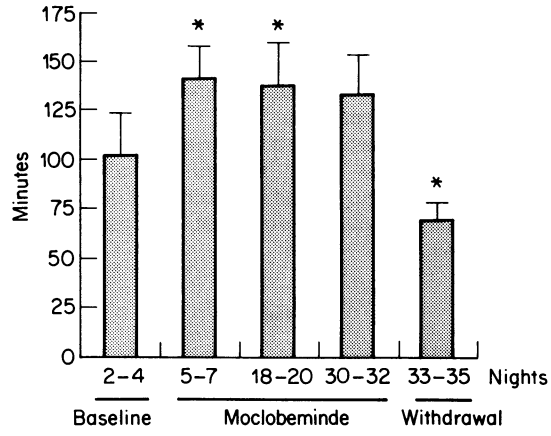

FIG. 8 REM sleep latency. $^{*}P < 0.05$.

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antidepressant effect appeared between the third and the fifth days, reaching a maximum at 10–23 days.

Analysis of the HRSD, Beck scale, and self-rating scale scores showed that there had been significant reductions in scores: at day 21, there was 58.4% reduction in the HRSD, 52.1% reduction in the Beck scale, and 49.5% decrease in the self-rating scale. Clinical impression thus confirmed a significant reduction in the severity of depression in the sample.

Neither systolic nor diastolic blood pressure (supine and standing) showed significant change during the administration of moclobemide. Blood, urine, and liver function tests showed no abnormal changes during treatment. Adverse events, which were all mild or moderate, included: a metallic taste in the mouth ($n=1$), mild stomatitis ($n=1$), blurred vision ($n=1$), anxiety ($n=1$), constipation ($n=1$), headache ($n=1$), urinary frequency ($n=2$) and oedema of the lower extremities ($n=1$).

Discussion

The irreversible MAOIs phenelzine and tranylcypromine abolish REM sleep and provoke an increase of as much as 250% above baseline on withdrawal (Le Gassicke *et al*, 1965; Akindele *et al*, 1970; Wyatt *et al*, 1971; Dunleavy & Oswald, 1973). In contrast, the antidepressant effect of moclobemide occurred despite the absence of a striking REM sleep suppressant effect. It could be argued that this difference between the drug's effects on mood and on REM sleep might be related to the selective blockade of MAO-A. However, cimoxatone — another selective and reversible MAO-A inhibitor — induces alterations in REM sleep which are similar to those of the older MAOIs (Hoff *et al*, 1986). Since moclobemide has a short plasma half-life, and the last dose in this study was taken at 18.00 hours, it is possible that the REM sleep suppressant effect had already disappeared by the time the patients arrived in the sleep laboratory. However, in the study by Steiger *et al* (1987), the last dose of the selective and short-acting MAO-A inhibitor, brofaromine, was taken at 12.00 hours, yet REM sleep was significantly reduced. An alternative possibility is that a mild direct REM suppressant effect was counteracted by the expected increase in REM sleep that normally occurs during recovery from depression.

Although the sample size was small, the direction of the data in this study appears to indicate that improvement in quality and architecture of sleep occurs concomitantly with improvement in symptoms of depression.

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