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REM Sleep Suppression Induced by Selective Monoamine Oxidase Inhibitors

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Abstract. The effects of 4 weeks of treatment with the selective monoamine oxidase (MAO) inhibiting antidepressants clorgyline and pargyline on the sleep of affectively disordered patients were studied. Both inhibitors resulted in near total suppression of REM sleep, a decrease in total sleep time, and an increase in the percent of stage 2 sleep. Clorgyline also increased awake time and decreased total recording period and sleep latency. In general, changes were greater for clorgyline than for pargyline and were about 50% slower to return to baseline after clorgyline compared to pargyline discontinuation. The results were consistent with the hypothesis that selective inhibition of the MAO type A, as produced by clorgyline, is sufficient to induce marked sleep changes. MAO inhibitor-induced receptor changes are proposed to account for the time course of the REM suppression and the REM rebound observed upon withdrawal.

Key words: Clorgyline – Pargyline – Receptors

Sleep disturbances form an integral part of the total symptomatology of depression (Mendels and Chernik 1975; Mendelson et al. 1977; Hawkins and Mendels 1966). Antidepressant drugs produce specific alterations of sleep patterns. The most prominent, perhaps, is that of REM sleep suppression, a property shared by lithium, the tricyclics, and monoamine oxidase inhibitors (MAOI) (Vogel 1975). Also, there has been some evidence that the extent of initial sleep changes produced by the tricyclics may predict antidepressant efficacy in individual patients (Kupfer et al. 1975; Gillin et al. 1978). As a result, detailed attention has been given to the potential usefulness of utilizing changes in sleep continuity and architecture for the subtyping and diagnosis of depression (Kupfer et al. 1975, 1979).

MAOI totally suppress REM sleep for long periods of time. Although MAOI fall into several classes, most of the sleep studies involving these drugs have been based upon the hydrazine (isocarboxazid, iproniazid, phenelzine) group. The more recently studied class of MAOI, the propargylamine derivatives, have not yet received detailed attention although they may be of particular interest from a mechanistic and clinical point of view, as some of the members of this class show promise to be selective inhibitors of the two specific types of MAO enzymes.

Clorgyline and pargyline, members of this class, preferentially inhibit in vitro the two forms of MAO, A and B, respectively, in the rat (Murphy 1978). The A form of MAO preferentially deaminates serotonin and norepinephrine and the B form has substrate preferences for phenylethylamine and benzylamine. As part of a comparison of their antidepressant efficacy and in vivo selectivity of these two inhibitors in humans, a detailed study of sleep changes was undertaken.

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Materials and Methods

Three males and five females (mean age 41.8 ± 11.5 years, range 24–61) were admitted to an affective illness research unit at the clinical center of the National Institutes of Health. The diagnosis of major affective illness in each of the patients was made on the basis of Research Diagnostic Criteria (Spitzer et al. 1978) with the aid of the Schedule for Affective Disorders and Schizophrenia (Endicott and Spitzer 1978). Seven patients were diagnosed as unipolar and one as bipolar. All patients were moderately to severely depressed at the time of entrance into the study. The patients gave informed consent to participate in a double-blind, randomized crossover study of clorgyline and pargyline, part of which included permission for sleep studies. Each trial consisted of a baseline (placebo) period of 4 weeks, a 4-week drug period, a 3-week placebo period, and a second 4-week drug period, followed by another placebo period. The order of clorgyline and pargyline administration was randomized. Clorgyline was given in doses of 20 mg/day initially and increased to 30 mg/day during week 1. The pargyline dose was 75 mg/day initially and then increased to 90 mg/day in week 1.

Sleep recordings were obtained during baseline (prior to drug administration) and during both drug and placebo periods. Four to nine baseline recordings were available for all patients. Two of the patients were studied on all nights during the drug trials, while the others were recorded only during week 4 of treatment with each drug and then continuously during a 14-day postdrug withdrawal period. Electrodes were applied nightly between 10–11:30 PM for recording of electroencephalogram, electrooculogram, and submental electromyogram. Patients were awakened at 7 AM if they had not spontaneously arisen already. Sleep records were read by a 'blind' investigator according to standard criteria (Rechtschaffen and Kales 1968). In addition to calculating the time spent in each of the sleep stages, these readings also provided sleep latency (time from lights out to sleep onset), REM latency (time from sleep onset to first REM period), and sleep efficiency (percent time on bed spent asleep) data.

For the analysis of data, only subjects who were able to complete the entire drug trial period with the full dose of

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Table 1
Clorgyline-induced sleep changes ($N = 8$)

	Baseline period	Clorgyline (week 4)	Postdrug withdrawal period	Probability
Sleep continuity (min ± SD)				
Sleep latency	43.5 ± 24.9	23.9 ± 9.7	28.3 ± 13.8	0.046
Early morning awakening	38.3 ± 27.6	40.7 ± 45.7	22.2 ± 13.8	NS
Awake time	35.5 ± 37.0	51.4 ± 22.2	43.6 ± 29.9	NS
Movement time	11.4 ± 8.8	18.9 ± 17.7	11.7 ± 9.4	NS
Total recording period	444.1 ± 18.0	374.5 ± 59.2	363.6 ± 69.6	0.003
Total sleep time	318.8 ± 49.0	262.2 ± 65.5	254.7 ± 75.0	0.014
Sleep efficiency (%)	71.8 ± 11.7	68.6 ± 9.7	68.7 ± 12.4	NS
Sleep parameters ± SD				
Stage 1 (%)	1.7 ± 1.4	2.4 ± 2.3	2.6 ± 1.8	NS
Stage 2 (%)	72.8 ± 13.5	93.2 ± 5.6	89.0 ± 12.6	0.0002
NREM time (min)	232.7 ± 46.8	260.8 ± 63.1	229.0 ± 42.8	NS
REM time (min)	75.3 ± 28.7	2.0 ± 3.3	38.1 ± 48.2	0.0003
REM (%)	23.4 ± 6.0	0.7 ± 1.1	10.4 ± 11.5	0.001

Table 2
Comparison of clorgyline- and pargyline-induced sleep changes ($N = 4$)

	Baseline	Pargyline (week 4)	Clorgyline (week 4)	Probability
Sleep continuity (min ± SD)				
Sleep latency	59.1 ± 25.0	49.3 ± 37.8	25.6 ± 9.1	NS
Early morning awakening	36.6 ± 25.7	25.2 ± 23.5	38.0 ± 16.8	NS
Awake time	15.8 ± 22.6	19.7 ± 15.6	49.8 ± 27.9	0.002
Movement time	14.5 ± 11.7	16.1 ± 14.5	28.3 ± 22.1	NS
Total recording period	442.0 ± 13.6	367.5 ± 57.9	370.3 ± 19.0	NS
Total sleep time	332.3 ± 24.7	276.0 ± 57.5	257.5 ± 25.5	0.027
Sleep efficiency	75.1 ± 8.2	75.2 ± 10.9	66.8 ± 8.4	NS
Sleep parameters ± SD				
Stage 1 (%)	1.4 ± 1.4	3.3 ± 1.3	3.1 ± 3.0	NS
Stage 2 (%)	72.8 ± 6.8	95.8 ± 2.1	96.2 ± 2.6	0.0006
NREM time (min)	253.4 ± 27.3	275.7 ± 57.6	257.5 ± 25.5	NS
REM time (min)	78.7 ± 21.7	0.5 ± 1.0	0.0 ± 0.0	0.002
REM (%)	23.8 ± 5.8	0.8 ± 0.2	0.0 ± 0.0	0.0001

30 mg/day clorgyline or 90 mg/day pargyline were included. Doses were reduced if side effects, usually orthostatic hypotension, developed. As a result only four of the sleep subjects completed the entire crossover trial, although another four completed the clorgyline and placebo periods. No significant correlations were observed between MAOI-induced sleep parameter changes and behavioral effects. The comparative behavioral effects of the drugs have been previously reported (Lipper et al. 1979).

Statistical evaluation utilized both a linear regression model and an analysis of variance model, with computations performed by means of the Biomedical Computer Programs (P series) packge. A P value greater than 0.05 was judged nonsignificant.

Results

The results are summarized in Tables 1 and 2. Four weeks of treatment with 30 mg/day clorgyline (Tables 1 and 2) and 90 mg/day pargyline (Table 2) resulted in a near total suppression of REM sleep. In addition, there was a decrease in total time asleep and an increase in the percent of stage 2 sleep during both drug treatment periods. Clorgyline alone significantly increased awake time and decreased total recording period and sleep latency. An increase in movement time on clorgyline was apparent but did not reach significance. In general, changes in each of the measures were greater for clorgyline than for pargyline treatment.

Sleep changes began to return to baseline values during week 1 of drug withdrawal, with the exception of awake time which increased during week 1 off drug, particularly for pargyline. Recovery from drug-induced changes in total sleep, REM time, REM percent, and stage 2 percent were nearly 50% slower for clorgyline than for pargyline, although the differences in this small sample were not statistically significant. Specifically, REM time during week 2 of withdrawal from clorgyline was only 44.5 min compared to a baseline of 78.7 min. Similarly, total sleep, awake time, and stage 2 percent had only partially returned to baseline during week 2 of withdrawal from clorgyline. However, only awake time did not significantly change during the 2-week withdrawal period.

Figure 1 illustrates the typical MAOI-induced REM changes in a single patient treated with clorgyline, and the REM rebound observed following withdrawal. A negative correlation of $r = -0.91$ ($P < 0.01$) was observed between REM latency and REM percent for this patient during week 1 of drug, whereas on baseline there was no significant correlation

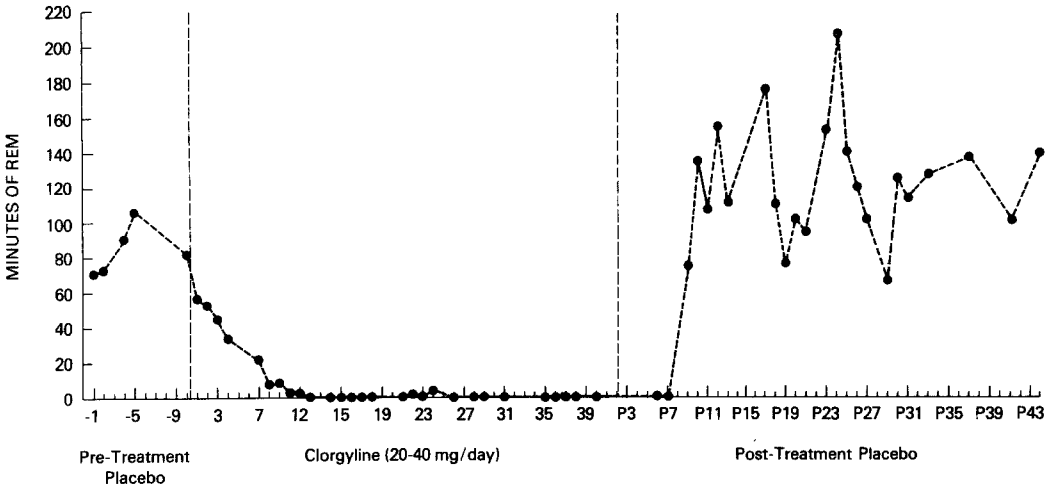

Fig. 1. The effect of clorgyline treatment on REM sleep in a single typical subject. The numbers on the *X*-axis represent the day of the drug trial. Negative numbers refer to days on placebo prior to clorgyline administration. Numbers preceded by a *P* refer to placebo days following clorgyline treatment

($r = -0.20$). The correlation coefficients for day of treatment with REM latency and REM percent were 0.64 and -0.59, respectively, suggesting that the correlation observed between REM latency and REM suppression was not merely a matter of the temporal relationship only. During baseline for this patient, REM latencies were 61.4 ± 14.8 min and REM percent $29.7 \pm 4.9\%$. By day 2 of clorgyline, REM latency was 143 min while REM percent was 21.7%. Similarly, for a second patient studied in detail, baseline REM latency (5.4 ± 4.9 min) changed by day 1 to 44 min and by day 2 to 75 min with only small changes in REM percent from baseline ($26.4 \pm 5.1\%$) to 28% and 17.2%.

Discussion

Overall, these results with MAOI of the acetylenic type (clorgyline and pargyline) are similar to those previously reported with the hydrazine class. Total REM suppression occurred in patients on about days 7–10 of treatment and REM rebound was observed about 10 days following withdrawal of the drugs (Akindele et al. 1970; Wyatt et al. 1969).

Substantial data from both in vitro and in vivo studies of rat brain MAO inhibition support the selectivity of clorgyline for the A form of the enzyme (Murphy 1978). Pargyline in vitro appears to be less selective in the rat (Campbell et al. 1979a). Our own data from the study of serotonin and norepinephrine metabolites, the quantitation of phenylethylamine and tyramine, and inhibition of platelet MAO-B suggests that, at the doses used in this study, clorgyline was again the more selective agent (Murphy et al. 1979, 1981). The two drugs, however, show very similar patterns of induced sleep changes. Of the two, clorgyline perhaps exhibited a more profound change which lasted somewhat longer after drug withdrawal. The results, then, are consistent with the hypothesis that inhibition of the A form of MAO is sufficient to produce the total suppression of REM, the reduction in total sleep time, the increase in percent of stage 2, and awake and movement time observed in our patients.

In contrast to the weaker REM-suppressive tricyclic antidepressants, MAOI have no known anticholinergic properties. Also, MAOI-induced REM suppression in rats is not reversed by physostigmine, a cholinergic agonist that attenuates tricyclic-induced prolonged REM transitions (Hill et al. 1980). These findings are, therefore, more consistent with alterations in catecholaminergic and/or serotonergic pathway input to sleep mechanisms as the responsible changes for the REM suppression observed during MAOI treatment. Doses of clorgyline similar to those used in this study increase both norepinephrine and serotonin concentrations within hours of a single dose in rats (Campbell et al. 1979a). Thus, the data are consistent with the previously hypothesized reciprocal relationships between REM sleep and catecholamines (Wyatt et al. 1971; Mendelson et al. 1977) and, in particular, the early increase in REM latency suggests a shift in noradrenergic-cholinergic balance (Jouvet 1972; Morgane and Stern 1974; Karczmer 1970) as REM latency appears to be inversely related to cholinergic activity (Sitaram et al. 1976).

The delayed onset of total REM suppression, however, with a temporal pattern similar to that of antidepressant activity, and the REM rebound following withdrawal suggests that the neurophysiological changes observed are at least partly the result of the same adaptive CNS changes that have been suggested to be important in the molecular mechanisms of antidepressant efficacy. For MAOI, these include receptor sensitivity changes observed both in animals (Campbell et al. 1979b; Cohen et al. 1982; Peroutka and Snyder 1980; Savage et al. 1980; Sellinger-Barnette et al. 1980) and in humans (Siever et al. 1981).

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