Psychopharmacology (1988) 95:S37–S43

Psychopharmacology

Effects of trazodone on the sleep of depressed subjects – a polygraphic study

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Abstract. The effects of 400–600 mg trazodone on the sleep patterns of ten depressed in-patients treated for 5 weeks were studied during the initial (days 1–3) and terminal (days 26–28) treatment periods. The sleep parameters were compared to those obtained from three sleep recordings performed just prior to the initiation of the treatment and after 2 adaptation nights at the end of a 2-week drug-free period. At the same time, the clinical evolution of patients was evaluated weekly using MADRS and Hamilton-Anxiety scales for anxiety-depression symptomatology and Spiegel and Norris sleep scales. Weekly blood samples were collected to measure plasma levels of trazodone and, at the end of the study, the elimination half-life at steady state was calculated by repeated measurements of plasma levels. Clinical improvement, as assessed by a reduction of more than 60% in MADRS scale scores, was accompanied by evidence of the definitely beneficial effects of trazodone on the disturbed sleep of these depressed patients. From the beginning of treatment, there was a hypnotic-like effect (increase in total duration of sleep and stage II, decrease in sleep latency and intrasleep awakenings). In addition, records at the end of the study showed an increase in delta sleep and an increase in REM latency, an effect classically associated with an antidepressant action. These particularly valuable effects of trazodone on sleep would suggest that this drug should especially be given in cases of depression with major insomnia.

Key words: Trazodone – Antidepressant – Polygraphic sleep recordings – Plasma levels – Refractory depression

Trazodone is an antidepressant whose structure is unrelated to currently marketed drugs of this type. It has a novel pharmacological profile.

Its central biochemical effects are characterized by an inhibition of serotonin uptake and a blocking action of alpha-adrenergic receptors, especially presynaptic alpha-2 receptors (Richelson 1983, 1984). When given chronically, a desensitization of beta-adrenoceptors and postsynaptic serotonin receptors occurs (Clements-Jewery 1978; Hingten et al. 1984).

The therapeutic properties of trazodone and its efficacy in treating depression have been substantially confirmed by a large body of double blind trials in comparison to tricyclic antidepressants such as amitriptyline and imipramine (Brogden et al. 1981–1984).

The activity of this substance is comparable to that of reference antidepressants. In contrast to the tricyclic family, trazodone presents neither anticholinergic activity (Gershon and Newton 1980) nor notable cardiovascular effects. In cases of overdose (Henry et al. 1984) almost a complete lack of cardiotoxicity has also been reported.

Classical pharmacological tests performed in animals have shown that trazodone has antiaggressive and sedative effects which are usually observed with anxiolytic molecules.

In sleep disorders either isolated (Montgomery et al. 1983) or accompanying depressive illness (Brooks et al. 1984; Wheatley 1984), the therapeutic efficacy of trazodone has been proved and is partially related to its sedative properties. There exist, however, only relatively few data on the concomitant neurophysiological effects, especially on EEG. The Montgomery study involved nine elderly volunteers complaining of poor sleep and treated for 3 weeks with 150 mg trazodone as a single dose in the evening. Together with a subjective improvement in the quality of sleep, the total duration of which was not increased, this study showed a reduction in both stage 1 sleep and the frequency of night-time awakenings while deep sleep was increased.

The Muratorio study (Muratorio et al. 1974) is to our knowledge the only one which reports on the effects of trazodone on the sleep recordings of depressed patients. After 7–10 days of treatment, there was a decrease in stage 1 sleep and an increase in stage 2 and 3 sleep. However, there was no report comparing the initial and middle-term effects of trazodone on the sleep patterns of depressed patients.

The aim of the present trial was to examine the initial and middle-term effects of trazodone administration on the sleep patterns of depressed patients already recorded after 2 weeks without any psychotropic treatment.

The therapeutic efficacy of trazodone is usually observed for dosages ranging between 150 and 450 mg, but reaching 600 mg in some patients. Considerable interindividual variations in plasma concentrations represent a handicap difficult to overcome since, in Mann's study (1981), the authors were unable to distinguish the plasma levels of responding patients (1.51 ± 0.29 μg/ml) from those who did not respond to a 4-week-long treatment (1.64 ± 0.17 μg/ml).

In order to try to solve the problem of efficient plasma concentrations of trazodone, our study was also aimed at defining a range of plasma concentrations resulting in the highest ratio of therapeutic antidepressant response/side effects. Trazodone pharmacokinetics investigated primarily

in healthy volunteers after a single dose showed a rapid and complete absorption after oral ingestion, with a C_{max} at 30–180 min (Brogden et al. 1984).

The half-life elimination of the substance ranged between 6.3 and 13 h (Bromet 1983, unpublished). The mean plasma concentration of trazodone after oral absorption of a dose of 125 mg is 1.46 ± 0.41 µg/ml 2 h after administration and 0.69 ± 0.36 µg/ml 6 h after.

Materials and methods

Ten depressed patients gave informed consent to participate in this clinical, pharmacokinetic and sleep polygraphic study.

Inclusion criteria involved in patients who filled RDC criteria of primary depression with a score higher than 20 in MADRS at the end of a wash-out period of 2 weeks for antidepressants and anxiolytics, 2 months for neuroleptics and 1 month for ECT.

Time course of the study

Control period. During a control period of 2 weeks the patients were submitted to standard clinical and laboratory tests (renal and hepatic, EKG, EEG, blood count, etc.) whose results had to be within normal limits.

Moreover, patients whose mood improved during this control period were discarded from the study.

Treatment period. These patients were treated with trazodone for 5 weeks. Monotherapy treatment began with one 100 mg tablet of trazodone on the 1st evening, then dosage was rapidly brought to the maximum between day 2 and day 4 (400, 500 or 600 mg in two or three daily administrations). A stable dosage for at least 1 week was required by the pharmacokinetic study. Dosages could be changed only on days 7 and 21.

Clinical measurements

Efficacy and tolerance were evaluated weekly using following scales:

- Depression scale: MADRS
- Hamilton anxiety scale
- Clinical global impression: CGI
- Notation of somatic symptoms: CHESS 84
- Spiegel and Norris sleep scales
- Overall sleep score (0: very poor, 10: excellent).

Weekly measures of blood pressure and heart rate were also carried out.

Pharmacokinetic measurements

Plasma concentrations of trazodone were determined weekly with blood samples drawn before the morning administration.

At the end of treatment (day 35), repeated measurements of blood concentrations 8, 12, 16 and 24 h after the last administration enabled the elimination curve of each patient to be constructed (after eliminating the noon and evening administrations) and to extrapolate the maximal concentration at equilibrium and the half-life elimination in conditions of chronic administration.

Assays were carried out with HPLC and detection was fluorometric (detection limit 0.050 µg/ml). The extraction method was similar to that used by Ankier et al. (1981).

Several types of analyses were carried out:

- Correlation studies by linear or nonlinear regression (Hill equation):
  therapeutic effects/plasma levels
  side effects/plasma levels
  ingested dose/plasma levels.
- Comparison at different measurement times of dosages and concentrations in terms of responders versus nonresponders (responders: decrease of MADRS score more than 50%).

Electroencephalographic measurements of sleep

Sleep was recorded at a paper speed of 5 mm/s according to standard leads (4 EEG, 1 EMG, 1 EOG and 1 EKG leads) with an additional respiratory monitoring (thoracic movements and upper airways flow). At the end of the study the recordings were scored visually on a 1 min time base according to Rechtschaffen and Kales criteria, the scorer being unaware of the location of the records within the development of the study.

Sleep recordings, preceded by 2 adaptation nights, were performed at the end of a drug-free period of 2 weeks during the 3 nights before – Control Period (C) – and the first 3 nights of treatment – Initial Period (I). Three more nights, again preceded by an adaptation night, were recorded at the end of the study – Terminal Period (T): days 26–28.

From each record the following parameters were computed and *t*-paired tests applied on the average values from each patient during each recording period:

- *Total Sleep Time* (TST) – including stage 1 sleep.
- *ST 1, ST 2, Delta* and *REM sleep* – respectively duration, expressed in min, spent in each of these sleep stages.
- *Sleep Latency* was calculated from the moment the lights were out to the beginning of the first episode of stage 2 sleep.
- *REM Latency* was calculated from the beginning of the first episode of stage 2 sleep.
- *Intra-sleep Wake* represents the number of minutes spent awake from the beginning of the first stage 2 episode to the end of the last episode of either sleep stage but stage 1.
- *Total Wake Time* was computed as the sum of Intrasleep Wake plus initial and terminal waking periods, the later being limited to 10 min.
- The *number of awakenings* was calculated on intrasleep wake.
- The *number of REM sleep episodes* was calculated considering two REM sleep episodes as distinct when 20 min at least apart.
- The *percentages of individual sleep stages* were expressed to TST.

Results

The study involved ten hospitalized patients (three men, seven women), mean age 48.4 ± 3.8 years. All scores at inclusion were higher than 28 in the MADRS scale. Various diagnoses and MADRS inclusion scores are shown in Table 1. The mean daily dosage at each examination is shown

Table 1. Study population

Patient	Sex	Age (years)	DSMIII diagnosis	MADRS inclusion score
CAP	M	57	296 22	35
CHA	F	27	296 33	37
VAR	F	56	296 32	24
MUL	F	36	296 22	35
SCH	M	60	296 23	29
MAR	F	41	296 32	35
FLA	M	35	309 00	27
CRO	F	55	296 32	39
RIBe	F	60	296 32	40
RIBo	F	56	296 32	29

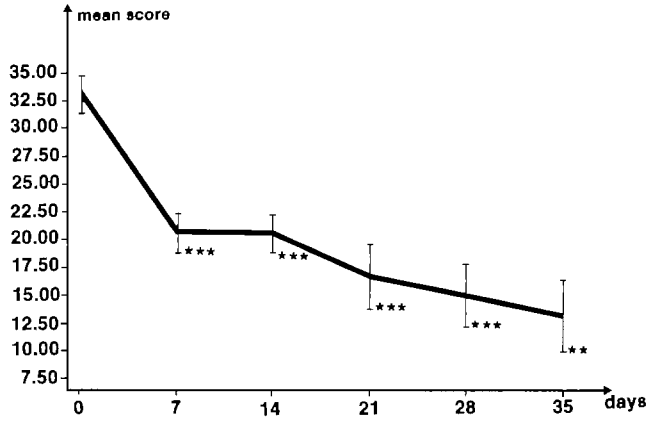

Fig. 1. M.A.D.R.S.
* $P<0.05$, ** $P<0.01$, *** $P<0.001$

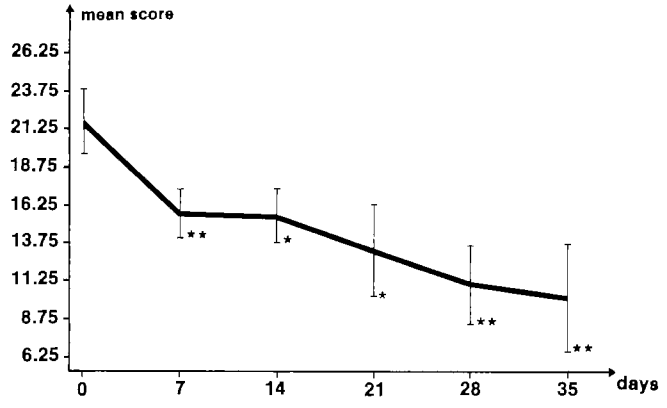

Fig. 2. Hamilton anxiety R.S.
* $P<0.05$, ** $P<0.01$, *** $P<0.001$

in Table 3. For five patients, all the daily dose (400 mg) was given in the evening.

Clinical study

The clinical evolution and the mean overall scores obtained with the different scales are shown in Figs. 1 and 2. From day 7 onwards, the decrease in these scores was highly significant.

The data involved nine patients only on day 35 due to the drop-out of one patient who had not improved after 4 weeks of treatment.

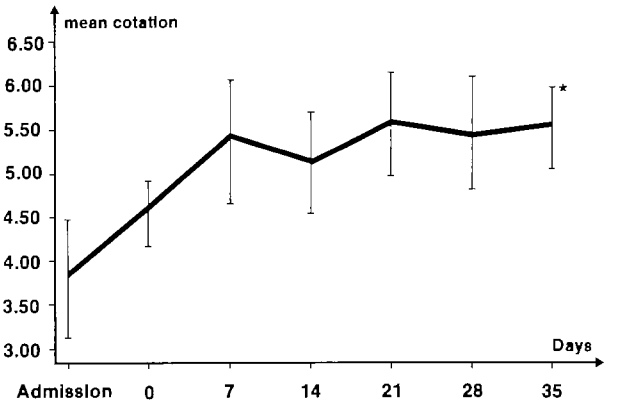

Fig. 3. Overall sleep score (grade: 0 to 10).
* $P<0.05$, ** $P<0.05$, *** $P<0.05$

Table 2. Clinical global impressions (number of patients of end point)

Efficacy	Tolerance			
	Undesired effects			
	Excellent tolerance	Mild side effects	Moderate side effects	Poor tolerance
Excellent	3 (4)	0 (2)	0 (1.33)	0 (1)
Good	0 (3)	3 (1.5)	1 (1)	0 (0.75)
Moderate	0 (2)	1 (1)	0 (0.67)	0 (0.50)
Poor	0 (1)	0 (0 5)	1 (0.33)	0 (0.25)

(Therapeutic risk-benefit index of tranzodone = 2.1)

Table 3. Plasma levels of trazodone

Days	Mean plasma levels (μg/ml)	Mean daily doses (mg)
7	1.637 ± 0.119	570
14	1.532 ± 0.173	470
21	1.571 ± 0.186	460
28	1.608 ± 0.159	420
35	1.584 ± 0.203	422

Concerning the overall sleep scores, the results in Fig. 3 show a tendency toward an improvement in sleep onset on day 7, which became significant only after 5 weeks of treatment. The small patient sample could explain this lack of significance at the initial period of treatment. Simultaneously there was an improvement, although not significant, in the scores of the different items of the Spiegel and Norris scales.

Finally, on day 35 the overall evaluation of treatment with CGI (Table 2) enabled a therapeutic index of 2.1 to be calculated, placing trazodone at the same level as the reference antidepressants.

The results were very good in seven patients, with side effects generally absent or very minor. Two patients, on the other hand, complained of more intense side effects including dizziness, tinnitus, nausea and edema.

Pharmacokinetic study

The analysis of concentrations measured at 8 a.m. showed that equilibrium was rapidly reached, regardless of dosage

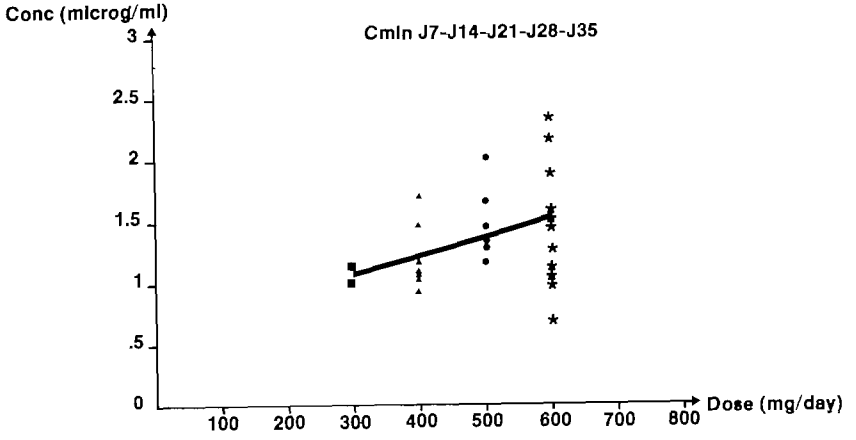

Fig. 4. Relationship between plasma levels and daily doses (t.i.d.). * 600 mg – $n=14$; • 500 mg – $n=8$; ▲ 400 mg – $n=8$; ■ 300 mg – $n=2$. Coeff $r=0.3839$; slope $=0.0015$; $P<0.05$

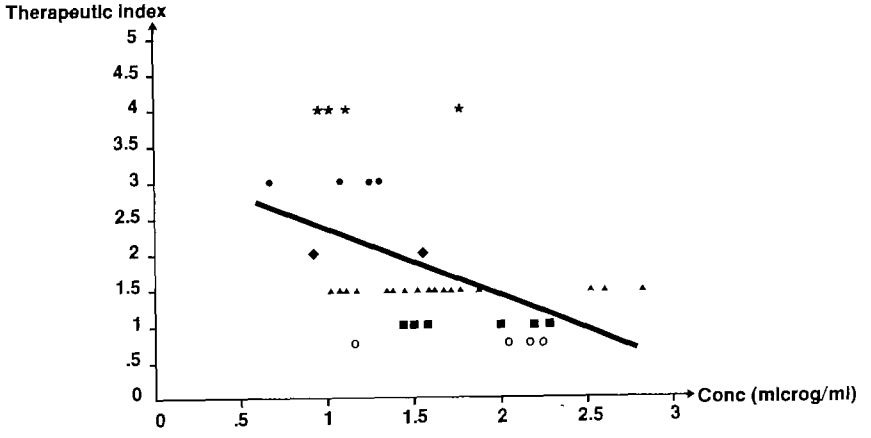

Fig. 5. Relationship between therapeutic index and plasma levels in responders. Coeff $r=0.4583$; slope $=0.9335$; $P<0.01$

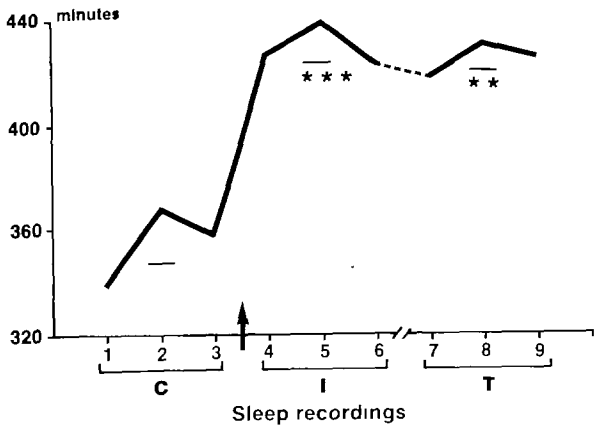

Fig. 6. Total sleep time. Sleep recordings: 1–2–3: Control period (D-3, D-2, D-1); 4–5–6: Initial period (D1, D2, D3); 7–8–9: Terminal period (D26, D27, D28). *Horizontal lines* correspond to the average values for each experimental period. Statistical differences with control values were evaluated using paired *t*-tests on the average values for each patient during each period of study. * $P<0.05$; ** $P<0.01$; *** $P<0.001$

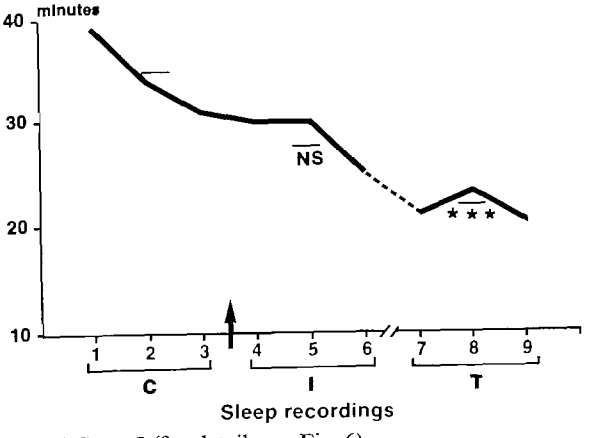

Fig. 7. Stage I (for details see Fig. 6)

adopted, since all concentrations measured on days 7–35 were identical, close to 1.60 µg/ml (Table 3).

The plasma half-life elimination calculated on day 35 (12.3 ± 1.1 h) was comparable to that reported in young healthy subjects. Calculated C_{max} was 5.80 ± 0.10 µg/ml after administering 200 mg trazodone on the average. Nevertheless, it should be noted that 12.00 µg/ml could be reached after administering 400 mg in a single dose. The true minimal concentration was close to 1.06 ± 0.10 µg/ml and probably corresponded to the effective minimal concentration obtained by dosage adaptation.

The linearity of trazodone pharmacokinetics was again verified in this study. For an identical rhythm of administration (3 per day) a significant relationship ($P<0.05$) existed between experimental plasma levels measured in the morning and the daily doses (Fig. 4).

In responders (good or very good therapeutic effects or basic scale score reduced by more than 50%), no correlation could be determined between plasma concentrations and the clinical effect, whether it was depression (MADRS scale), anxiety (Hamilton scale) or sleep (score 0–10). In

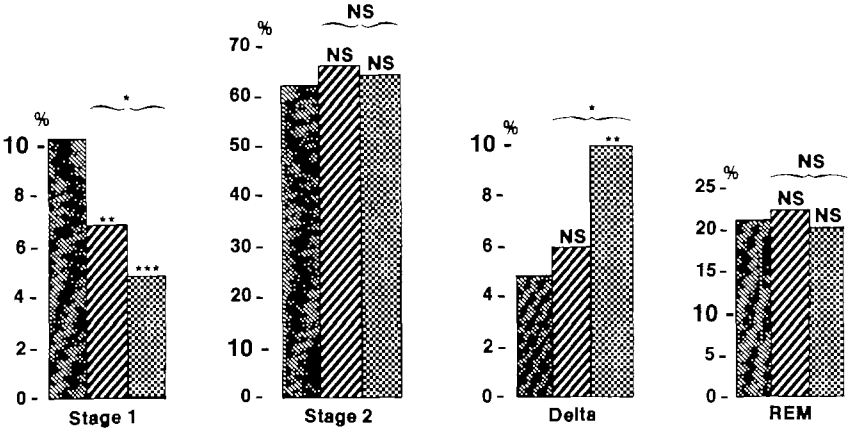

Fig. 8. Percentage of the different stages/TST. ▨ C; ▨ I; ■ T

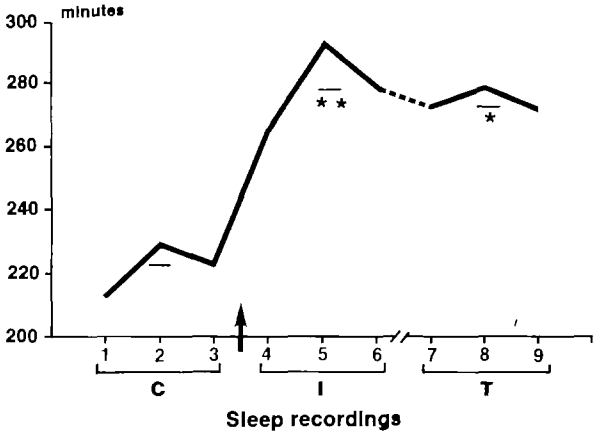

Fig. 9. Stage II (for details see Fig. 6)

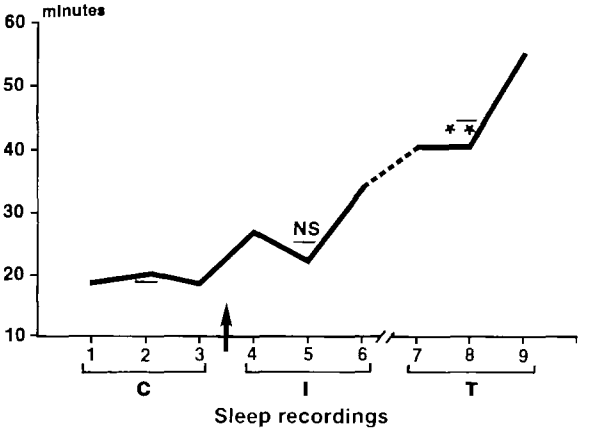

Fig. 10. Delta (stages III and IV) sleep (for details see Fig. 6)

fact, efficacy was obtained for concentrations between 1.00 and 2.50 µg/ml.

On the other hand, in the same responders a significant relationship ($P < 0.01$) between the therapeutic index and plasma concentration measured in the morning led to the definition of a zone of effective and well tolerated concentrations (therapeutic index from 2 to 4) and to another of concentrations remaining effective but less well tolerated (therapeutic index from 0.75 to 1.5); the limit is probably around 1.5 µg/ml (Fig. 5). The therapeutic index was calculated from the experimenter's evaluation of the treatment, in terms of the clinical effect and any side effects observed (CGI).

No conclusive result was obtained in terms of a concentration leading to poor tolerance, as a result of high intersubject variations in the very small population of this study.

Finally, the theoretical concentrations which may be obtained in a 68-kg depressed subject were calculated for the most often encountered treatment, i.e. one tablet in the morning, one at noon and two in the evening. Under these conditions, mean plasma concentrations for the three daily administrations would be 1.63 µg/ml (minimum) to 4.52 µg/ml (maximum).

Electroencephalography

TST increased as soon as during the 1st treatment night and remained so during all the recorded nights. This led to a highly statistically significant increase, as compared to the control period during both treatment periods (Fig. 6).

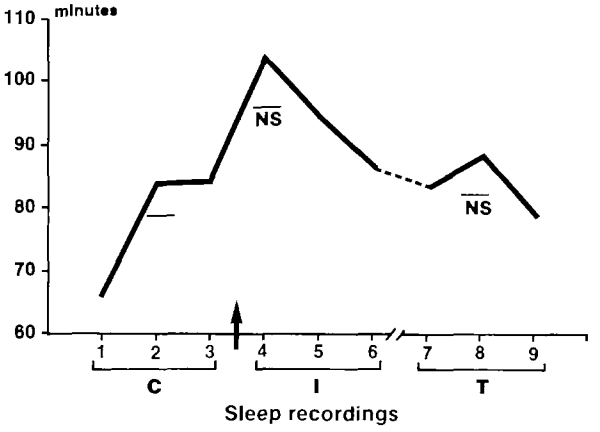

Fig. 11. REM sleep (for details see Fig. 6)

As shown in Fig. 7, there was a progressive reduction in stage 1 sleep which became highly significant during the T period while stage 1 percentage to TST (Fig. 8) was reduced during both I and T periods.

The significant increase in stage 2 sleep which took place from the beginning to the end of the treatment was not accompanied by an increase in its percentage to TST (Figs. 8 and 9).

On the 3rd treatment night delta sleep started to increase and remained so during the terminal treatment period, when it was significantly ($P < 0.01$) increased as compared

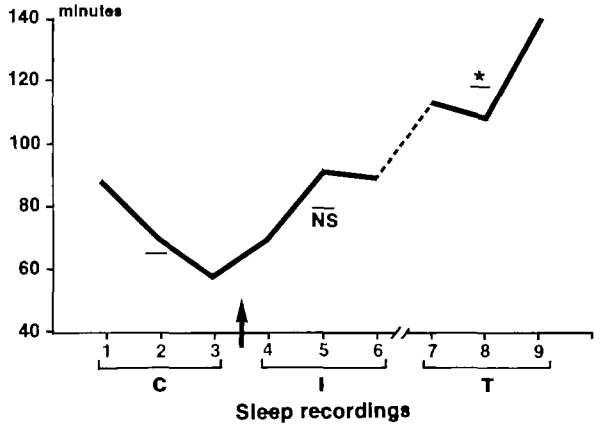

Fig. 12. REM latency (for details see Fig. 6)

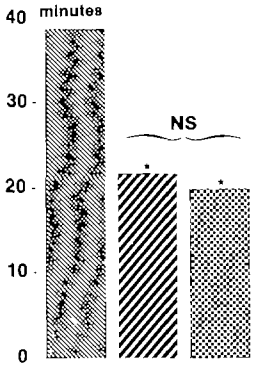

Fig. 13. Sleep latency. ▧ C; ▨ I; ■ T

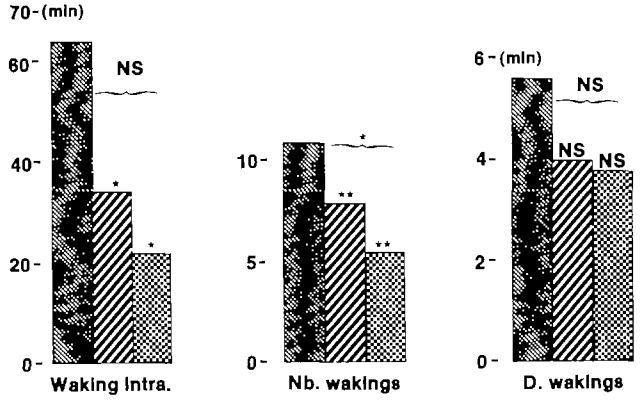

Fig. 14. Intra-sleeping waking. ▧ C; ▨ I; ■ T

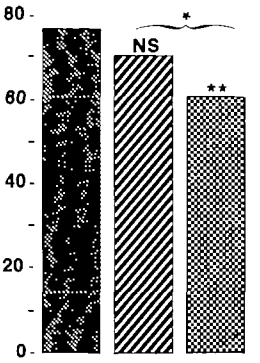

Fig. 15. Number of stage shifts. ▧ C; ▨ I; ■ T

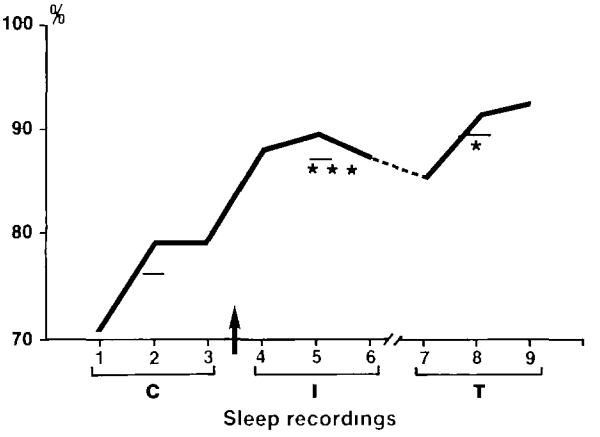

Fig. 16. Sleep efficiency index (for details see Fig. 6)

to the control period. The same applied for its percentage to TST (Figs. 8 and 10).

Whatever period was neither REM sleep time nor REM percentage was affected by the treatment, even though a clear increase in this sleep stage took place on the 1st treatment night (Figs. 8 and 11). It is interesting to notice that REM latency was virtually unchanged at the beginning of the treatment and that it was only during the last part of the study that it was enhanced by a significant amount (Fig. 12).

Sleep latency was significantly shortened during both treatment periods ($P=0.014$ and $P=0.035$) as was intra-sleep wake, the reduction of which was linked to a clear decrease in the number of awakenings (Figs. 13 and 14) without significant change in their average duration. The number of stage shifts was significantly reduced at the end of the treatment (Fig. 15). As a consequence of most of the above-reported changes, the sleep efficiency index was significantly improved during both treatment periods (Fig. 16).

Discussion

One puzzling feature from our data is the short delay necessary to observe a clinical improvement. This is somehow surprising when compared to the classical 10–20 days' lag necessary for the clinical action of antidepressants. A possible explanation could be that the initial doses of trazodone were high, thus leading to some side effects (nausea, dizziness) in several patients. This initial worsening of symptoms could have triggered or been the sign of a rapid post-synaptic down-regulation of receptors.

Control recordings provided evidence for the existence of most of the classical polygraphic criteria of depression since during at least one recording out of three, the REM latency of each patient in the study was shorter than 40 min. Moreover, TST (including stage 1 sleep) was, on average, less than 6 h, including stage 1 sleep. Delta sleep amounts

averaged 20 min only, whereas intrasleep-wake duration was longer than 60 min. None of these patients had any qualitative or quantitative symptoms of dopamine-dependent depression (Mouret et al. 1987) or sleep apneas.

The methods used in this study through recordings performed at the very beginning and at the end of a 28-day treatment period allowed us to compare the initial and middle-term effects of trazodone on sleep patterns of depressed patients. This is of interest, since some sleep parameters were modified as early as during the first 3 days of treatment while for some others this occurred later.

Among the early modifications TST enhancement, together with that of stage 2 sleep, is an interesting one since it started on the very 1st night of treatment. At the same time, sleep latency and intrasleep wake were reduced, thus suggesting a clear hypnogenic-like effect. These rapidly occurring signs of sleep improvement did not adapt during the study.

By contrast, those sleep parameters most related to depression were significantly modified during the terminal period of treatment only. This was the case for REM latency, delta sleep duration and percentage to TST as well as for the time spent in stage 1 sleep, even though for the latter its percentage to TST was reduced from the early treatment period. No change was observed on the duration and percentage to TST of REM sleep.

As reviewed by Vogel (1983), REM sleep deprivation was, and still is, thought to be the mechanism of action of antidepressant drugs, although this REM sleep suppressive effect does not occur with iprindole (Baxter and Gluckman 1969) or viloxazine (Brezinova 1977). According to our data, trazodone should be added to these peculiar drugs whose effects suggest that the REM sleep suppressant effect of most antidepressant products might well represent the consequence, and not the mechanism of their antidepressant effects (Mouret 1982).

Interestingly, as compared to the other non-REM sleep-suppressing antidepressant products, trazodone stands in quite a peculiar position. Viloxazine administration together with the persistence of REM sleep, the latency of which is enhanced, is accompanied, as opposed to trazodone administration, by an increased sleep latency and a decrease in Total Sleep Time. As a matter of fact, trazodone's effects upon sleep parameters are very similar to those of lithium carbonate as far as delta sleep is concerned (Chernik and Mendels 1974) but quite different when considering REM sleep, since the latter is reduced after lithium carbonate administration. It thus appears that trazodone is the first antidepressant drug whose hypnogenic properties appear unrelated to REM-reducing effects.

One of the most important feature in this context is that these sleep-recorded improvements occurred as soon as the first administration night and that they persisted after a middle-term period of administration.

Such an effect suggests that one of the major indications of this new product should be depression with major insomnia and, possibly, resistant insomnia.

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