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Effects of Single and Multiple Doses of Dexnafenodone, Imipramine and Placebo on Sleep of Young Healthy Volunteers

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The effects on polygraphically recorded sleep of single and repeated doses of dexnafenodone (20 mg daily) were determined in 12 young, healthy subjects, and compared to those of imipramine (75 mg daily: six subjects) and placebo (six subjects). After two adaptation nights, sleep was recorded at baseline (night 0), and after the first (night 1) and last (night 5) evening administration of the study drugs. REM sleep was substantially inhibited in both nights under the two active treatments, whereby the effect appeared immediately. With the exception of slow wave sleep (SWS), which was more reduced in night 1 under imipramine than under dexnafenodone, the other sleep stages were essentially unchanged. Time awake during bed rest increased under both active treatments, with a more rapid increase under dexnafenodone. Dexnafenodone, a potent inhibitor of noradrenaline, and to a lesser degree of serotonin reuptake, induced changes in the pattern of sleep which are comparable to those of non-sedating tricyclic antidepressants. The mode of action as well as the pharmacodynamic profile of dexnafenodone led to the expectation that this new substance will show antidepressive activity on a clinical level.

KEY WORDS—dexnafenodone; imipramine; antidepressant drugs; sleep; REM sleep

INTRODUCTION

Dexnafenodone is a phenylsubstituted tetrahydronaphtalenone derivative which proved effective in animal models for antidepressants. Compared to other antidepressant drugs dexnafenodone has a novel chemical structure. It is an enantiomerically pure drug with (S)(+)-configuration. Dexnafenodone is a highly potent inhibitor of synaptosomal noradrenaline and serotonin uptake. The noradrenaline uptake inhibition being about eight times more marked than the serotonin uptake inhibition. The *in vitro* potency of dexnafenodone is greater than that of imipramine by a factor of about 2 to 3 (Knoll AG brochure). The substance has been found to inhibit noradrenaline uptake *in vivo* as well (inhibition of α-methyl-metatyrosin-induced noradrenaline depletion). The affinity to muscarinic (M_1), histaminergic (H_1) or serotonergic ($5HT_2$) receptors, which are typically affected by tricyclic antidepressants, is very low or absent. *In vivo* studies showed no evidence of anticholinergic or antihistaminergic activity, i.e. no effect on pupil size and salivation, and no sedation.

Kinetic investigations after single and multiple dose adminstration showed that dexnafenodone reached maximum plasma concentrations 5 h post-administration. Concentrations declined approximately monoexponentially with half-lives of about 25 h.

The objective of the present investigation was to study the effect of single and multiple dosages of dexnafenodone on polygraphically recorded sleep of young healthy volunteers and to compare it with the effect of the tricyclic antidepressant imipramine. The target parameter was REM sleep latency, which is increased by most antidepressants (Gillin, 1983). It was tested whether dexnafenodone has REM sleep depressing potency comparable to that of imipramine.

MATERIALS AND METHODS

Subjects

Twenty-four male, healthy subjects participated in the study. All subjects gave written informed consent for participation. Twelve of them (mean age: 27·9±3·5 years) were treated with dexnafenodone, six (mean age: 30·2±4·8 years) with

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imipramine, and six (mean age: 26·8 ± 4·5 years) with placebo. Standard inclusion/exclusion criteria were employed for subject safety and to omit conditions which might bias the outcome of this polysomnographic study. All volunteers were normal sleepers with a normal distribution of sleep stages. Two weeks before and during the study subjects were asked to abstain from any other medication to avoid interaction effects. During study days consumption of alcohol, caffeine and nicotine was not allowed.

Experimental design

The study was performed double-blind, placebo-controlled according to a randomized two-factorial parallel group design with three medication conditions (dexnafenodone, imipramine, and placebo). Subjects were assigned randomly to the treatment factor (dexnafenodone, $n_1 = 12$; imipramine, $n_2 = 6$; placebo, $n_3 = 6$). The second factor was the duration of treatment with the observational nights 0, 1 and 5. The baseline night (N_0) was preceded by two adaptation nights in the sleep laboratory. Night 1 (N_1) and night 5 (N_5) were the recording nights after the first and the last dosage.

Medication

The study medication (20 mg dexnafenodone, 75 mg imipramine and placebo) was administered orally once daily at 21.00 h for five consecutive days. To ensure double-blind conditions, the treatment units were administered as gelatine capsules, which were identical in shape and colour for all treatment units.

Polygraphic recording

Sleep biosignals (EEG, EMG, EOG and ECG) were recorded for 8 h from 23.00 h to 07.00 h and amplified with conventional polygraphs (analogue filtering: time constant TC = 0·03 s and low pass filter Fc = 70 Hz for EEG; TC = 0·015 s and Fc = 200 Hz for EMG; TC = 1·2 s and Fc = 15 Hz for EOG; TC = 0·03 s and Fc = 30 Hz for ECG). Gold electrodes were fixed to the scalp with collodium and to the face with adhesive tape. The recordings were stored on paper. The polysomnographic data were visually analysed according to the standardized criteria for sleep scoring (Rechtschaffen and Kales, 1968) by an expert independent of the recording team. The following sleep parameters were computed.

- Sleep onset latency (SOL, in minutes). SOL was defined as the interval between light-out and the first 30-s epoch of stage 2 sleep.
- REM sleep latency. REM latency was defined as the interval between SOL and the first 30-s epoch of REM sleep (RL, in minutes).
- Total sleep time (TST, in minutes). TST was defined as the sum of all epochs of sleep, including movement time (MT).
- Time awake (minutes and percentage of time in bed, TIB).
- REM sleep time (minutes and percentage of TIB).
- Sleep stage 1 (minutes and percentage of TIB).
- Sleep stage 2 (minutes and percentage of TIB).
- Slow wave sleep, SWS (minutes and percentage of TIB). SWS was defined as the combined sleep stages 3 and 4.

Target parameters for statistical analysis were *REM sleep latency* and *REM sleep time*. All other parameters were considered as secondary variables. Tolerability and safety of the pharmacological treatments were controlled by measuring blood pressure and ECG. Adverse events were assessed with an 88-item symptom list.

Statistical analysis

Statistical analysis was performed with a two-factorial ANOVA for unbalanced sample sizes with dependent measurements on the treatment factor. The factor *duration of treatment* was statistically tested with a conservative F test according to Greenhouse and Geisser to regard deviations from a Gaussian distribution and non-homogeneity of variance–covariance matrices. The critical p-value for statistical significance was set as 5 per cent.

To estimate effect size, the differences between the mean values of N_1 and N_5 and the baseline night N_0 were divided by the value of N_0;

$$\text{Effect size} = \frac{(N_1 + N_5)/2 - N_0}{N_0}$$

RESULTS

Time awake increased significantly from N_0 to N_5 by about 30 to 50 min for dexnafenodone and imipramine. In the placebo group there was an unexpected increase in mean time awake N_5 caused

by a single subject who had a sleep duration of less than 3 h in N_5 (Table 1). The effect of the factor treatment duration was significant in the analysis of variance ($p = 0{\cdot}007$). The differences between treatments were not significant for any measurement time. Total sleep time (TST) showed an inverse trend with a reduction of about 30 to 45 min in N_5. The effects of the factor treatment duration was significant for TST ($p = 0{\cdot}005$). While the general decrease was significant, this was not the case for the differences between the three treatment groups.

REM sleep latency at baseline (N_0) was in the range of 60–80 min for all three treatment groups. While it remained constant across the three study nights under placebo, REM latency increased two- to four-fold higher mean values in the first and last treatment night with dexnafenodone and imipramine. The effects of the two factors, treatment and treatment duration as well as the interaction between both factors were significant in the analysis of variance ($p < 0{\cdot}01$). The lengthening of REM latency was accompanied by an increase in scatter, which reflects the discontinuous distribution of REM latencies (Table 1).

A closer inspection of the distribution of REM latencies showed that all but one were shorter than 120 min in N_0. This was also true for N_1 and N_5 in the group treated with placebo, while the number of latencies less than 120 min decreased to a minimum under active drug treatment. Under dexnafenodone the number of REM latencies less than 120 min was 11/12 (92 per cent) for N_0, 3/12 (25 per cent) for N_1 and 0/12 (0 per cent) for N_5. Under imipramine the values were 6/6 (100 per cent) for N_0 and 1/6 (17 per cent) for nights N_1 and N_5.

REM sleep time decreased by about 70–80 min between N_0 and N_1 for dexnafenodone and for imipramine. The reduction remained constant between N_1 and N_5. Both active treatments were significantly different from placebo, which showed only a small reduction of about 20 min between N_0 and N_5 (Figure 1). For this parameter the effects of the two factors, treatment and treatment duration as well as the interaction between both factors were significant in the analysis of variance ($p < 0{\cdot}01$).

SWS was reduced by about 40 min against baseline in N_5 under imipramine, while it remained rather constant under dexnafenodone. The placebo-treated group showed a slight decrease of about 15 min between N_1 and N_5 (Figure 1). Although the effect on the factor, treatment duration was

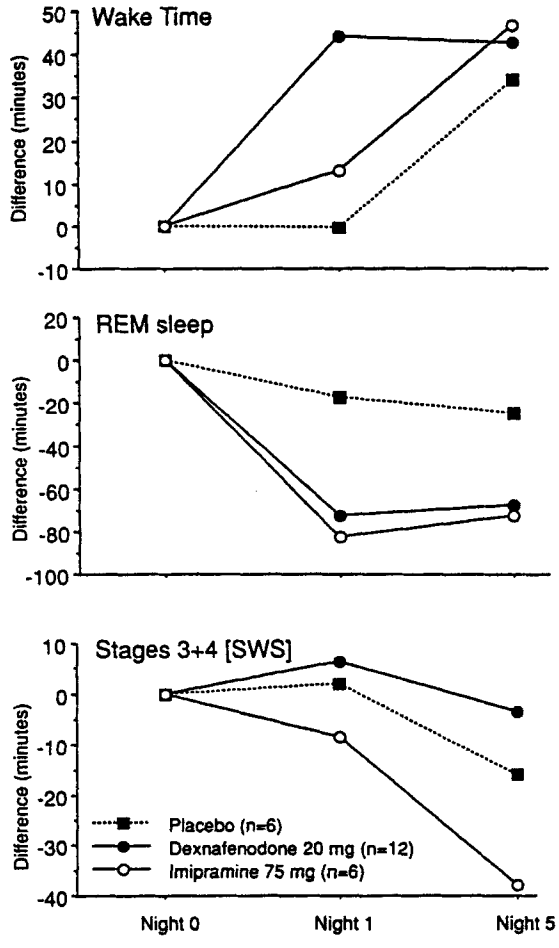

Figure 1. Changes of polysomnographic parameters after single (N_1) and repeated (N_5) administration of dexnafenodone (20 mg/day; solid circles), imipramine (75 mg/day; open circles) or placebo (squares) in comparison to baseline (N_0). Difference values are presented for time awake (upper panel), REM sleep (middle panel), and SWS (lower panel)

significant ($p = 0{\cdot}03$), differences between treatments did not become significant, mainly due to the large inter-individual differences in SWS amount, which were already present at baseline. In contrast to SWS, the amount of the nonREM sleep stages 1 and 2 changed only slightly under active treatment, with a tendency for sleep stage 2 to increase.

The values of effect size, which are given in Table 1, demonstrate the most pronounced changes for REM sleep latency, time awake, and REM sleep time under treatment with dexnafenodone and imipramine. REM latency increased by about 150 per cent and REM sleep decreased by about 70 per cent under dexnafenodone. The

Table 1. Mean values (standard deviations), and effects size for different polysomnographic parameters for dexnafenodone, imipramine and placebo

		Wake [min]	REM [min]	S1 [min]	S2 [min]	SWS [min]	TST [min]	REM Lat. [min]	SOL [min]
Dexnafenodone	N_0	31·3 (20·0)	102·4 (18·6)	41·2 (16·2)	259·9 (25·8)	48·1 (27·0)	455·6 (20·5)	83·9 (27·1)	24·3 (15·4)
($n_1 = 12$)	N_1	75·9 (54·8)	30·8 (19·2)	53·2 (17·2)	262·9 (36·4)	55·8 (35·6)	407·6 (55·2)	192·6 (114·6)	19·2 (9·7)
	N_5	74·9 (62·2)	34·6 (20·6)	52·0 (17·0)	275·3 (41·0)	43·9 (38·1)	410·3 (62·4)	226·6 (67·2)	33·6 (24·5)
Effect size (%)		140·6	−68·1	27·7	3·6	3·6	−10·2	149·0	8·8
Imipramine	N_0	28·6 (24·6)	114·2 (20·0)	44·3 (10·5)	227·4 (30·9)	66·2 (30·0)	457·2 (24·9)	60·8 (10·5)	26·3 (27·1)
($n_2 = 6$)	N_1	43·1 (18·8)	32·3 (16·4)	52·9 (18·6)	292·9 (33·6)	57·7 (30·8)	442·2 (18·6)	247·8 (98·3)	17·1 (12·3)
	N_5	76·2 (13·1)	41·8 (13·0)	51·1 (8·2)	283·8 (23·0)	28·8 (23·5)	409·0 (11·7)	161·6 (47·2)	34·6 (27·1)
Effect size (%)		108·6	−67·5	17·5	26·8	−34·7	−6·9	237	−1·6
Placebo	N_0	49·8 (71·7)	104·8 (33·6)	45·3 (16·1)	216·9 (39·8)	65·8 (18·0)	436·8 (71·7)	79·3 (16·0)	35·3 (46·7)
($n_3 = 6$)	N_1	48·1 (31·9)	86·3 (13·6)	47·3 (24·9)	231·9 (31·4)	67·7 (25·2)	435·3 (33·0)	77·4 (23·3)	32·8 (35·8)
	N_5	83·8 (110·4)	80·9 (31·2)	52·1 (25·6)	213·8 (74·2)	50·3 (27·1)	399·2 (111·5)	69·1 (8·8)	39·3 (35·0)
Effect size (%)		32·3	−20·2	9·6	2·7	−10·4	−4·5	−7·6	2·1

N_0 indicates the baseline night, N_1 the first night after treatment, and N_5 the night after 5 days of treatment. Effect size is expressed as a percentage.

respective values for imipramine were 240 per cent and 70 per cent, while only minor changes were observed under placebo.

All subjects completed the study as planned. The incidence rate of adverse events was significantly higher under dexnafenodone (1·8 per subject and measurement point) or imipramine (rate 1·3), compared to placebo (rate 0·4). The most frequently reported symptoms were dry lips, head pressure, increased sensitivity to light, tiredness and feeling uncomfortable.

DISCUSSION

The results show that dexnafenodone displays effects on sleep polygraphy which are similar to those of imipramine, which was used in this study as a reference drug with well-established antidepressive properties (Herrington and Lader, 1981). Both substances increased REM latency and reduced REM sleep time in a comparable manner, suggesting that dexnafenodone displays a profile which is comparable to that of tricyclic antidepressants with inhibitor activity in noradrenaline reuptake. Some studies in depressed patients suggest that the extent of initial REM sleep inhibition correlates positively with the later clinical response to tricyclic antidepressants (Kupfer *et al.*, 1976; Gillin *et al.*, 1978; Höchli *et al.*, 1986). Despite such observations, the question as to whether or not inhibition of REM sleep is essential for the induction of antidepressive activity (Hartmann, 1968; Vogel, 1975) is controversial. Results of trimipramine, a drug with a complex pharmacological profile, are inconclusive. While Nicholson *et al.* (1989) observed a reduced duration of REM sleep after acute administration of trimipramine, other authors found no effect of the drug on REM sleep (Ware *et al.*, 1985; Wiegand *et al.*, 1986).

The finding that TST decreased and time awake increased with imipramine confirms results on the arousing effect of imipramine in depressed patients (Nicholson *et al.*, 1989). Dexnafenodone showed a similar pattern in the present study. Finally, there may be a difference between the two substances in relation to SWS. After repeated dosing SWS was more strongly inhibited in night 5 by imipramine than by dexnafenodone.

It has been suggested that the occurrence of REM sleep critically depends on the balance between aminergic and cholinergic mechanisms (McCarley, 1982; McCarley and Massaquoi,

1992). In the case of both dexnafenodone and imipramine an increase in primarily noradrenergic activity might be responsible for a reduction of REM sleep by a shift in this balance.

In conclusion, the sleep polygraphy model has proved efficient at delineating the pattern and time course of the effects of dexnafenodone, a substance with presumably antidepressive potential.

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