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Effects of Nocturnal Doses of Mirtazapine and Mianserin on Sleep and on Daytime Psychomotor and Driving Performance in Young, Healthy Volunteers

J. G. RAMAEKERS*, N. D. MUNTJEWERFF, L. M. A. VAN VEGGEL, M. M. C. UITERWIJK and J. F. O'HANLON
Experimental Psychopharmacology Unit (formerly Institute for Human Psychopharmacology), Brain & Behaviour Institute, Maastricht University, Maastricht, The Netherlands

Eighteen healthy volunteers participated in a randomized, double blind, cross-over trial. They received mirtazapine, mianserin or placebo during separate periods of 15 days. Mirtazapine and mianserin were respectively administered in doses of 15 mg and 30 mg nocte for the first 7 days and doses of 30 mg and 60 mg nocte for the remaining 8 days. Assessments were made at baseline and on days 2, 8, 9 and 16 of each period to compare effects of drugs and placebo on mood, psychomotor (CTT, CRT, CFF and Vigilance) and 'actual' driving performance. Sleep quality and duration and side-effects were assessed at baseline and every treatment day. Mirtazapine 15 mg and mianserin 30 mg slightly impaired psychomotor and driving performance on day 2 of treatment. On day 8, the effects were virtually gone, although some driving impairment could still be observed in the mianserin condition. No drug effects on performance were found on day 9 despite the dose escalation. On day 16 of treatment, driving performance and vigilance slightly decreased in, respectively, the mirtazapine and the mianserin conditions. These effects indicate that tolerance to the drugs' adverse effects was not complete. This observation was also supported by subjective data. Similar increments in sleep duration and feelings of lethargy, drowsiness and weakness were observed throughout treatment with both drugs. Alertness and contentedness was always lower during both drug treatments than with placebo. Spontaneously reported adverse events were similar to self-rated side-effects and more of both were recorded during mianserin treatment. It is concluded that the acute and subchronic effects of nocturnal doses of both drugs were similar and equally low in magnitude. Effects on performance were much less than those seen in other studies after administration during the day. Full daily doses of both drugs should be prescribed in nocturnal dosing regimens, and not in divided doses over the day, for avoiding excessive sedation and performance impairment.

KEY WORDS — mirtazapine; mianserin; sleep; driving performance; impairment; psychomotor function

INTRODUCTION

Mirtazapine is a new piperazinoazepine antidepressant. Its chemical structure is similar to mianserin but its mechanism of therapeutic action differs (De Boer and Ruigt, 1995; De Boer, 1996; Kelder *et al.*, 1997). Both drugs have strong binding affinities for presynaptic α_2 adrenergic auto- and heteroreceptors as well as postsynaptic serotonergic 5-HT_2, 5-HT_3 and histaminergic H_1 receptors where they act as antagonists of the endogeneous ligands. Neither has any affinity for muscarinic receptors and mirtazapine, in contrast to mianserin, has little for α_1 receptors. The blockade of α_2 autoreceptors on noradrenergic neurons enhances the synthesis and release of noradrenaline. The enhanced rate of noradrenaline release stimulates α_1 receptors on serotonergic neurons and subsequently enhances serotonergic cell firing. Further facilitation of 5-HT release is caused by mirtazapine's antagonistic activity at α_2 heteroreceptors located at axonal terminals of serotonin neurons. By specific blocking both post

*Correspondence to: Dr. J. Ramaekers, EPU, Brain & Behaviour Institute, Department of Psychology, Maastricht University. P.O. Box 616, 6200 MD Maastricht, The Netherlands. E-mail: j.ramaekers@psychology.unimaas.nl. Website: http://www-np.unimaas.nl/PsyPharm

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synaptic 5-HT_2 and 5-HT_3 receptors the net effect of mirtazapine within the serotonergic system is to indirectly enhance neurotransmission at 5-HT_1 receptors. The remaining site of antagonistic mirtazapine activity, the H_1 receptor, is not thought to mediate an antidepressant effect. Rather H_1 blockade causes sedation that may be desirable or unwanted depending upon the patient's condition and when the drug is taken during the circadian cycle. Mirtazapine is rapidly absorbed and reaches T_{max} within 2 h. The drug undergoes substantial 1st pass metabolism resulting in about 50% bioavailablity (Voortman and Paanakker, 1995). The contribution of the active metabolite to the total pharmacodynamic profile of mirtazapine is relatively low, i.e. 3–6% (Delbressine and Vos, 1997). Elimination of the parent and its active metabolite occur with a half-life of 20–40 h. Steady state is reached within 3–5 days of continual, once daily dosing (Timmer *et al*., 1995). The therapeutic dose range is 15–45 mg/d. Mirtazapine is generally given at night to promote sleep and avoid unwanted daytime sedation.

Phase I tolerabity trials (Data on file) showed that single doses of 15, 30 and 45 mg mani produced mild to moderate sedation that appeared to be dose-related in healthy volunteers. Postural hypotension and consequently dizziness were found after doses of 30 and 45 mg. Repeated ascending doses up to 60 mg caused subjective feelings of sedation at all levels, but postural hypotension dissipated with developing tolerance. The effects of single doses of mirtazapine on psychomotor performance and sleep were investigated in two studies. Mattila *et al*. (1989) administered morning doses of mirtazapine 15 mg, amitriptyline 50 mg and placebo alone and in combination with 15 mg diazepam to 12 young, healthy volunteers. Mirtazapine impaired performance in several tests of psychomotor performance (Tapping, CFF, Maddox wing, Postural Instability) and increased feelings of drowsiness and passiveness between 1, 5 and 6 h post drug. The investigators judged the degree of impairment after mirtazapine to be about equal to that of amitriptyline. Neither drug's effect was potentiated by diazepam. Ruigt *et al*. (1990) investigated the effects of a single dose of 30 mg nocte on sleep and psychomotor performance in a placebo controlled study involving six healthy volunteers. EEG recordings showed a reduction in nocturnal waking and an increase in deep, slow-wave sleep. Psychometric tests (Reaction time and Vigilance) conducted the next morning at 16 h post drug showed no effect of mirtazapine. Subchronic effects of mirtazapine on psychometric performance were studied in a pilot study by Robbe *et al*. (1994). Six volunteers were treated with ascending evening doses of 15, 30 and 45 mg for 19 days. Two other volunteers received placebo in parallel. Moderate impairment was found between 12 and 17 h after the initial dose on almost every psychometric test (CFF, Tracking, Divided Attention and Vigilance). Subsequent doses did not affect performance, indicating that the development of tolerance occurred at a faster rate than the ascention of mirtazapine's plasma concentration. However, subjective feelings of drowsiness persisted throughout the treatment period.

These studies suggest that whatever impairing potential mirtazapine might have, it is mitigated in whole or part by nocturnal dosing and sleep. Because patients following the recommended dosing regimen will take the drug in this manner it seemed essential to determine what the drug's effects on performance are over the days following nocturnal dosing. This study was designed for that purpose. It compares the effects of ascending doses of mirtazapine, with equipotent doses of mianserin and placebo on psychomotor and actual driving performance in healthy volunteers. Mianserin was chosen as an active control because of its well known sedative potential (Seppällä, 1977; Curran and Lader, 1986; Mattilla *et al*., 1978), but also because it is in structure most related to mirtazapine. Effects on performance were expected to differ between drugs if their differential affinities for α_1 adrenoreceptors is a determining factor.

METHODS AND MATERIALS

Subjects

Eighteen healthy volunteers, nine males and nine females, were recruited by newspaper advertisements. Initial screening was accomplished on the basis of replies to a medical history/driving-experience questionnaire. Qualified individuals were physically examined by the Medical Supervisor who also obtained blood samples and a standard 12-lead electrocardiogram from each one. Standard blood chemistry and hematology assays were conducted on those samples. Subjects were included if they satisfied the following criteria: possession of a valid driver's licence, aged 21–35 years, normal binocular visual acuity,

corrected or uncorrected. Exclusion criteria were as follows: excessive smoking, positive urine drug screen at screening, history of psychotic illness, drug abuse, cardiovascular disease, unusual sensitivity to medicinal drugs, renal, hepatic or neurological disease. The study was carried out in accordance with the World Medical Association's declaration of Helsinki (Hong Kong Modification, 1989). It was approved by the standing Ethics Review Committee of Maastricht University. Written informed consent was obtained from each subject prior to participation.

Design and treatments

Treatments were administered in separate 15-day series, according to a placebo controlled, 3-way, double-blind, cross-over design. Treatment orders were originally balanced and assigned to subjects by exhaustive random selection from six independent 3×3 Latin Squares. Subjects received the following treatment regimens during respective treatment periods: mirtazapine 15–30 mg, mianserin 30–60 mg and placebo. Dosing started the evening before (day 1) the first test day (day 2). Subjects received 15 mg of mirtazapine and 30 mg of mianserin during the first seven days of treatments, and respectively 30 and 60 mg on subsequent days. Drugs and placebo were always ingested at fixed times in the evening. At baseline and on days 2, 8, 9 and 16 of each treatment series, subjects undertook a sequence of performance tests and subjective assessments of mood according to a fixed schedule, between 15 and 18 h following the evening dose.

Performance assessments

Training occurred in two sessions prior to application of treatments. Training in Critical Fusion Frequency (CFF), Critical Tracking (CTT) and Choice Reaction Time (CRT) continued until the subject had performed each one with less than 5% of the variance from the average measured over the final three trials. Performance on the sustained attention test (VIG) and the standard Highway Driving Test show little practice effects, so for these, training simply involved the administration of one trial.

CFF (Hz) is the visual system's threshold for repeatedly responding to and recovering from discontinuous (on–off) light stimulation. Trains of stimuli arriving at the retina at frequencies below the CFF threshold are perceived as flicker, those above, as constant light (Vuurman *et al*., 1991).

CTT measures the subject's ability to control a displayed error signal in a 1st-order compensatory tracking task. Error appears as horizontal deviation of a cursor from midpoint on a horizontal, linear scale. The subject is required to make compensatory joy-stick movements that null the error by returning the cursor to the midpoint. The frequency of cursor deviations, and therefore its velocity, increases as a stochastic, linear function of time. The subject is required to make compensatory movements with a progressively higher frequency. Eventually this response frequency lags the error signal by 180°. At that point the subject's response adds to, rather than subtracts from, the error and control is lost. The frequency at which the subject loses control is commonly defined as lambda-c (the 'critical frequency'). The reciprocal of this frequency is theoretically the perceptual/motor delay for humans operating in closed-loop system. As such it is analogous to a 2-choice reaction time in discrete responding tasks. The subject performed this test in five trials on each occasion. The mean lambda-c (rad/s) was recorded as the final score (Jex *et al*., 1966).

CRT (ms) measures the subject's average reaction time to the words 'left' and 'right' using corresponding push-buttons. Half of each type are presented at compatible and incompatible (i.e. left and right) position on a computer display. Average reaction time was scored over 48 trials.

VIG has been extensively used in studies on human vigilance performance (Mackworth, 1950). Subjects are seated in front of a computer screen displaying a circular arrangement of 60 dots simulating the second marks on a clock. Dots are briefly illuminated in clockwise rotation at a rate of one per second. Usually the rotation proceeded with a 6° 'jump'. Subjects are instructed that at rare, irregular intervals the target proceeds with a 12° jump by skipping one of the dots in the normal sequence. This 'double jump' is the signal to which subjects respond by pressing a button. The dependent variable of the test is the number of correct detections; the test lasts 45 min.

The Highway Driving Test has been used for drug screening purposes in The Netherlands since 1981 (O'Hanlon *et al*., 1982). It was standardized the following year and has been applied in essentially the same manner ever since. The subject's task is relatively simple. He/she enters a primary highway (4-lane, divided) at the beginning

of a 100 km circuit. He/she then proceeds to drive while attempting to maintain the vehicle at a constant speed (95 km/h) and steady lateral position between the delineated boundaries of the slower traffic lane. The subject is allowed to deviate from this procedure in order to pass slower vehicles travelling in the same lane. At an intersection halfway through the circuit, the subject drove off the highway and re-entered travelling in the opposite direction.

The subject was accompanied by two investigators. A technician, whose task was to operate the equipment, was present in the rear passenger's seat. A licenced driving instructor was seated in the front passenger's seat with access to dual controls. His sole function was to ensure test safety. Subjects were instructed to operate safely at all times and that the treatments might affect their ability to do so. They were informed of their legal responsibility to stop a test in progress if feeling for any reason that to continue would be unsafe. They were further informed that they would be asked to stop by the instructor if, in his opinion, their physical appearance or driving performance indicated the possibility of a control loss. In the event that a subject chose to stop or was told to do so by the instructor, he/she was required to first signal and then bring the vehicle to a gradual halt on the paved shoulder of the road.

Several electronic signals indicating the driver–vehicle–road interaction were automatically recorded during the test. The most important was acquired by an electro-optical device which continuously measured the lateral distance separating the vehicle and the left lane-line. This signal was digitized at a rate of 4 Hz and stored on an on-board computer disk file for later editing and analysis. The off-line editing routine involved removal of all data segments that revealed signal loss, disturbance or the occurrence of passing manoeuvres. Clean data were then reduced within successive 5 km segments to yield corresponding means and variances for lateral position. The square root of the variance pooled over all segments, or total standard deviation of lateral position (SDLP), was then taken as the dependent variable for the Highway Driving Test.

Assessments of mood

A series of 16, 100 mm horizontal visual analog scales were used to subjectively evaluate changes in mood experienced by the subject as a result of the treatment. Subjects were asked to indicate how they felt at the time of testing by drawing a vertical line on each scale; the ends of each scale represent the opposite extremes of a given state (drowsy–alert, tense–relaxed, etc.). The subject was told that each scale represents the entire spectrum of each mood state. The result was measured in mm from the right end of the scale. Using this test, three factors, i.e. alertness, contentedness and calmness can be calculated on the basis of a main component analysis (Bond and Lader, 1974).

CNS and sleep assessments

Side-effects were recorded by subjects on separate 100 mm visual analogue scales. The items included drowsiness, lack of concentration, memory disturbances, dizziness, nausea, weakness, headache, lack of coordination, dry mouth and lethargy. Sleep was assessed by subjects using the Groning Sleep Questionnaire (Mulder-Hajonides van der Meulen, 1981). This is a standard clinical sleep quality questionnaire describing the quality and duration of sleep. Sleep questionnaires were completed following waking on baseline and days 2–16 of treatment. Side-effects were assessed in the evening of the same days. For analytical purposes they were later averaged over three assessment days to construct five consecutive time periods that covered the whole treatment. Averages were made over days 2–4, 5–7, 8–10, 11–13 and 14–16.

Pharmacokinetics

Blood samples were collected on days 2, 8, 9 and 16 of treatment. Mean plasma concentrations were determined by capillary Gas Chromatography with Nitrogen-Phosphorous-selective Detection (GC-NPD). Extraction from alkalinized plasma was performed with *n*-hexane. The limit of quantification was 0·2 ng/ml.

Statistics

Analyses were carried out by means of the SPSS/PC + program series to investigate whether the effects of mirtazapine and mianserin on performance differed from those of placebo (H_0). Performance during treatment was adjusted for initial differences at baseline by means of a standard analysis of covariance. Adjusted scores of psychomotor and driving performance and mood were analyzed at every time point using a

two factor ANOVA (Subjects and Treatment). Mean-contrast (drug versus placeco) tests were conducted for measuring the significance of contributions of each, individual drug to the overall Treatment effect. These specific drug–placebo comparisons were made independently of the corresponding overall effect. This is a legitimate procedure if the comparisons are built into the design or suggested by the theoretical basis for the experiment (Winer, 1962). The pooled within subject residual variance was used as the error term for conducting all tests within a particular set.

Adjusted means of sleep parameters and subjective side-effects were not normally distributed. They were analyzed by the non-parametric Friedman test to detect main differences between treatments and placebo. These were followed by Wilcoxon's signed-rank tests to compare the effects of treatments and placebo on separate treatment days.

RESULTS

Drop-outs

One subject withdrew from the second period after 10 days of mianserin treatment. Another subject stopped participation prior to his third period, in anticipation of a possible recurrence of side-effects he had experienced during the first period (mianserin), i.e. apathy and loss of libido. Consequently, both subjects did not participate in the third period wherein they would have been treated with mirtazapine. In total 16 subjects completed the study.

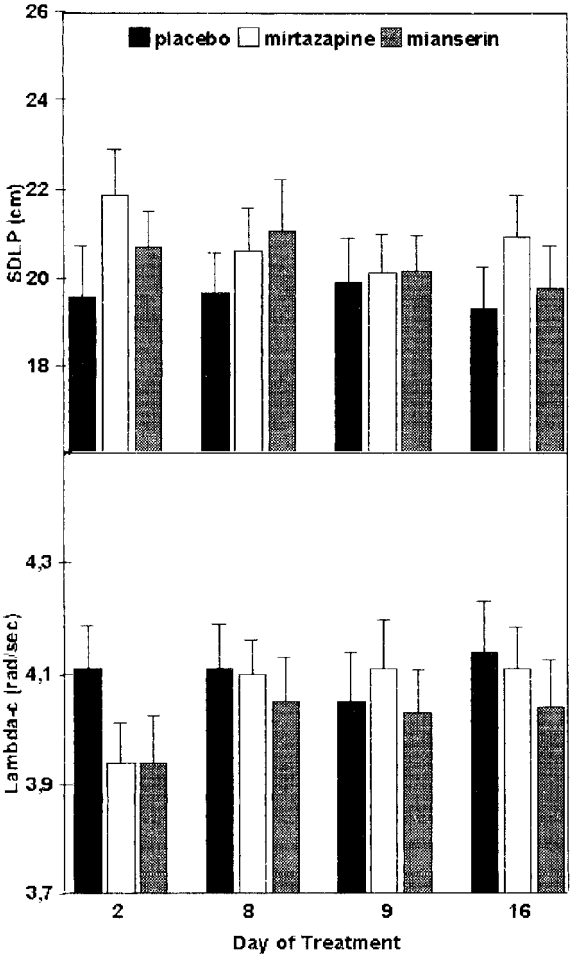

Figure 1. Mean (SE) SDLP (upper panel) and lambda-c (lower panel) adjusted for baseline on days 2, 8, 9 and 16 of treatment

Psychomotor and driving performance

Summary of significant and nearly significant results from the statistical analyses are given in Table 1. Treatment effects on CTT and SDLP reached significance on day 2 and days 2 and 9 respectively. Drug–placebo comparisons revealed impairing effects on CTT of both drugs on day 2 of treatment. They also showed elevated SDLP values on day 2 and 16 of treatment with mirtazapine and on day 8 with mianserin, though the latter just failed to reach significance. Mean (SE) CTT and SDLP values in every treatment condition are shown in Figure 1. Mianserin also decreased the number of correct detections in the sustained attention test on day 2 of treatment. On day 16, the effect of mianserin on sustained attention approached significance. CFF and CRT never differed between treatments.

Mood

The overall Treatment effect on alertness was always significant except on day 8. The effect of Treatment on contentedness was also significant on days 2 and 9. No effect of Treatment was found on calmness. Drug–placebo comparisons on separate days revealed decrements in alertness on all test days during treatment with mianserin. Mirtazapine also decreased alertness but its effects only approached significance on days 2, 9 and 16 of treatment. Contentedness decreased on day 2 and 9 of treatment with mianserin and on days 9

Table 1. Summary of significant and *nearly significant* treatment effects on psychomotor and driving perfortmance and mood as indicated by ANOVA (drug–placebo differences were always indicative of impairment)

Test	Day	ANOVA Overall			Mirtazapine vs placebo		Mianserin vs placebo	
		df	*F*	*p*	*F*	*p*	*F*	*p*
CFF (Hz)	2	–	–	–	–	–	–	–
	8	–	–	–	–	–	–	–
	9	–	–	–	–	–	–	–
	16	–	–	–	–	–	–	–
CTT (rad/s)	2	2,32	4·50	0·019	6·27	0·018	7·00	0·013
	8	–	–	–	–	–	–	–
	9	–	–	–	–	–	–	–
	16	–	–	–	–	–	–	–
CRT (ms)	2	–	–	–	–	–	–	–
	8	–	–	–	–	–	–	–
	9	–	–	–	–	–	–	–
	16	–	–	–	–	–	–	–
VIG (%)	2	–	–	–	–	–	4·43	0·043
	8	–	–	–	–	–	–	–
	9	–	–	–	–	–	–	–
	16	–	–	–	–	–	*3·20*	*0·083*
SDLP (cm)	2	2,32	*3·07*	*0·060*	6·00	0·020	–	–
	8	–	–	–	–	–	*4·01*	*0·054*
	9	–	–	–	–	–	–	–
	16	2,31	3·64	0·038	6·89	0·013	–	–
Alertness (mm)	2	2,32	4·30	0·024	*3·37*	*0·076*	8·30	0·007
	8	–	–	–	–	–	4·76	0·037
	9	2,32	4·05	0·027	*3·18*	*0·084*	7·59	0·010
	16	2,31	5·95	0·007	*4·05*	*0·053*	12·0	0·002
Contentedness (mm)	2	2,32	3·54	0·041	–	–	6·24	0·018
	8	–	–	–	–	–	–	–
	9	2,32	5·37	0·010	4·69	0·038	9·73	0·004
	16	–	–	–	4·31	0·046	–	–
Calmness (mm)	2	–	–	–	–	–	–	–
	8	–	–	–	–	–	–	–
	9	–	–	–	4·65	0·039	–	–
	16	–	–	–	–	–	–	–

and 16 of treatment with mirtazapine. Calmness decreased on day 9 of treatment with mirtazapine. An overview of all significant or nearly significant Treatment effects on performance and mood parameters is shown in Table 1.

Subjective sleep estimations

Both mirtazapine and mianserin increased estimated sleep duration over their entire period of administration ($\chi_9 = 36{\cdot}12$ and 43·93, respectively; $p = 0{\cdot}000$). The separate drug's effects on sleep duration were present, more or less constantly, within every successive 3-day period. Most comparisons between periods of drugs and placebo treatment were significant. On the average, subjects slept 43·2 and 42·6 min longer during treatment with mirtazapine and mianserin than while taking placebo.

An apparent difference was noted between the drugs' effects on the group's impression of how well they had slept. Despite the increase in sleep duration, similar for both drugs, they rated their overall sleep quality as about the same with mirtazapine and somewhat worse with mianserin as compared to placebo. The latter difference was significant over all treatment nights ($\chi_9 = 19{\cdot}45$; $p = 0{\cdot}021$) and almost for the first three nights,

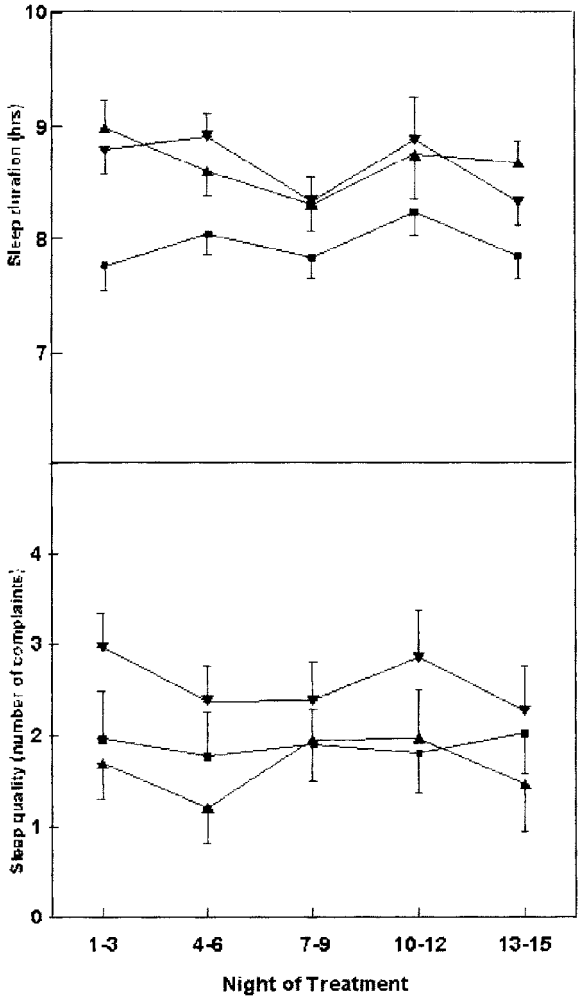

Figure 2. Mean (SE) sleep duration (upper panel) and sleep quality (lower panel) adjusted for baseline throughout every treatment period. Symbols indicate the following treatments: placebo, ■; mirtazapine, ▲; mianserin, ▼

tested separately ($Z = -1{\cdot}88$; $p = 0{\cdot}059$). Mean (SE) sleep duration and quality throughout every treatment condition are shown in Figure 2.

Subjective side-effects

The following self-rated side-effects significantly differed between each drug and placebo: drowsiness, weakness, memory disturbances, lethargy, headache, dry mouth, dizziness and concentration problems ($\chi_9 > 20{\cdot}46$; $p < 0{\cdot}015$). In addition, mianserin increased uncoordination and nausea ($\chi_9 > 27{\cdot}89$; $p < 0{\cdot}001$). Drug–placebo comparisons over successive 3-day intervals showed that mianserin and mirtazapine similarly increased feelings of lethargy throughout treatment ($Z < -2{\cdot}39$; $p < 0{\cdot}016$); drowsiness (Figure 3) during four out of five intervals ($\chi < -2{\cdot}00$; $p < 0{\cdot}045$); weakness between days 2 and 10 ($Z < -1{\cdot}99$; $p < 0{\cdot}046$) and difficulty concentrating between days 2 and 4 ($Z < -2{\cdot}05$; $p < 0{\cdot}039$). Dry mouth and dizziness were respectively greater than placebo levels between days 2–13 and 2–10 of mianserin treatment ($Z < -1{\cdot}92$; $p < 0{\cdot}055$) and between days 2–7 and 5–7 of mirtazapine treatment ($Z < -2{\cdot}02$; $p < 0{\cdot}043$). Headaches were more prevalent between days 8–13 of mianserin treatment ($Z < -2{\cdot}11$; $p < 0{\cdot}035$) and days 5–7 and 11–13 of mirtazapine treatment ($Z < -1{\cdot}96$; $p < 0{\cdot}049$).

Overall frequencies of spontaneously reported adverse events are summarized by treatment in Table 2. In total, 127 complaints were judged by the Medical Supervisor to be treatment-related. Multiple adverse events were reported by only one or two subjects within the same treatment periods. The types of events were similar after both drugs, but somewhat more frequent following mianserin. During mirtazapine treatment, adverse events reported by more than two subjects were: Fatigue (11×), drowsiness (12×), dry mouth (4×), cold, dizziness and difficulty concentrating (3×). During mianserin treatment they were: fatique (17×), drowsiness (11×), dry mouth (6×), dizziness (5×), difficulty concentrating, tension in arms or legs (4×), and headache (3×). During placebo treatment there were few reports of adverse events, mainly headache (4×) and fatigue (3×).

Pharmacokinetics

Mean (SD) plasma concentrations for mirtazapine on respective treatment days were 6·55 (2·18), 11·87 (3·77), 17·86 (5·83) and 23·30 (9·59) ng/ml. Mean plasma concentrations (SD) of mianserin were 7·71 (3·02), 16·14 (9·66), 24·21 (12·80) and 35·39 (21·38) ng/ml.

DISCUSSION

The main purpose of this study was to determine whether ascending doses of mirtazapine and mianserin have any impairing effects on behaviour. Results from psychomotor and driving tests showed that impairment was most evident after the initial doses of mirtazapine 15 mg and mianserin 30 mg. On day 2, both drugs impaired

Table 2. Treatment related adverse events as judged by the Medical Supervisor, rate of occurrence and numbers of subjects (%) complaining of each symptom in every treatment condition

	Mirtazapine	Mianserin	Placebo
Abdominal cramps		1 (5·56)	
Depressed		1 (5·56)	
Diarrhoea		1 (5·56)	
Difficulty concentrating	3 (18·75)	4 (22·22)	
Difficulty focusing eyes	1 (6·25)		
Difficulty waking up	1 (6·25)		1 (5·56)
Disturbance of equilibrium		1 (5·56)	
Dizziness	3 (18·75)	5 (27·78)	
Drowsiness	12 (75·00)	11 (61·11)	
Dry mouth	4 (25·00)	6 (33·33)	1 (5·56)
Fatigue (during daytime)	4 (25·00)	7 (38·89)	1 (5·56)
in the morning	3* (12·50)	3 (16·67)	
in the afternoon		1 (5·56)	
in the evening	4 (25·00)	6 (33·33)	2 (11·11)
Headache	1 (6·25)	3 (16·67)	4 (22·22)
Apathy		1 (5·56)	
Increased appetite	1 (6·25)		
Muscle spasm in legs	1 (6·25)		
in arms		1 (5·56)	1 (5·56)
Nausea	2 (12·50)	1 (5·56)	
Pain in legs		1 (5·56)	
in arms		1 (5·56)	
Palpitations	1 (6·25)		
Tension in legs		3 (16·67)	
in arms	1 (6·25)	1 (5·56)	
Shakiness	2 (12·50)	2 (11·11)	
Vomiting		2 (11·11)	
Muscular weakness		1 (5·56)	
Catch a cold	3 (18·75)		1 (5·56)
Sore throat	1 (6·25)		
Flu symptoms		1 (5·56)	
Loss of interest		1 (5·56)	
Weight gain		1 (5·56)	
Intracranial pressure		1 (5·56)	
Total complaints	48 (37·80)	69 (54·33)	10 (7·87)
Total subjects complaining of any symptom	14 (87·50)	17 (94·44)	7 (30·39)

*This complaint was reported by the same subject twice. Other complaints were reported only once per subject per treatment.

tracking performance, whereas driving and vigilance performance deteriorated after treatment with mirtazapine and mianserin respectively. All mean differences, however, were very small. The increase in SDLP of 2·2 cm after the first dose of mirtazapine was less than that shown by 'social drinkers' taking the test with a blood alcohol concentration (BAC) of 0·5 mg/ml (Louwerens *et al.*, 1987). This is an important comparison since epidemiological research has shown that BAC $\leqslant$0·50 mg/ml is not associated with an elevated risk of fatal traffic accidents (Borkenstein *et al.*, 1964). The implication is that neither drug's effects on driving performance in this study were of sufficient magnitude to reduce the safety of vehicle operation.

By day 8, little evidence of treatment effects were still present, although some driving impairment (increase in SDLP of 1·4 cm) could still be observed in the mianserin condition. Escalation of the dose did not affect performance on day 9. On day 16, however, mirtazapine and mianserin again produced some impairment, the former in the driving, and the latter in the vigilance test. Impairment on this day was still low in magnitude and not greater than the respective acute effects. These

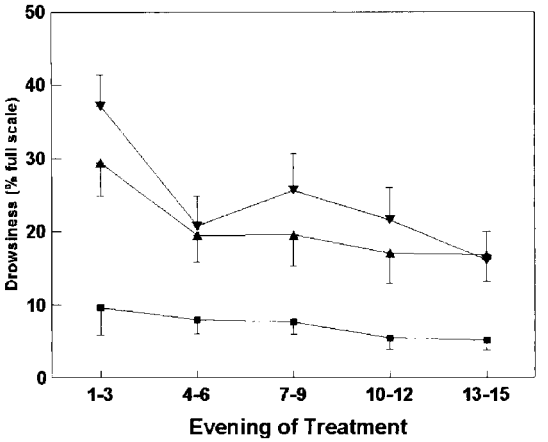

Figure 3. Mean (SE) drowsiness adjusted for baseline throughout every treatment period. Symbols indicate the following treatments: placebo, ■; mirtazapine, ▲; mianserin, ▼

results indicate that doubling the doses of both drugs after a week on medication produces no greater impairment than seen after the initial dose. Following these dosing regimens, mianserin and mirtazapine effects were always just above or below detection thresholds of comparably sensitive driving or psychomotor tests. For this reason one should pay less attention to the fact that both drugs affected performance in different tests at different times and more to fact that both drugs impaired performance to the same extent throughout treatment. These effects cannot be ignored, but neither do they appear to be a source of special concern.

Mianserin's and mirtazapine's effects on performance in this study were clearly less in magnitude than those found previously. As mentioned in the Introduction, Mattila *et al.* rated the effects of a single dose of mirtazapine 15 mg on psychometric performance similar to those of amitriptyline 50 mg. Similarly, acute and repeated doses of mianserin 10 mg have been found to seriously impair psychomotor performance (Seppällä, 1977; Curran and Lader, 1986; Mattila *et al.*, 1978). Elevations in mean SDLP, three times as high as in the current study, have been found after administration of mianserin 10 mg tds by investigators employing the same driving test (Louwerens *et al.*, 1986; Ramaekers *et al.*, 1992). In the latter study, mean mianserin plasma concentrations prior to driving were almost the same (i.e. mean and range of 13, 7–18 mg/ml versus 8, 4–14) as those found in the current study. It is therefore very unlikely that mianserin's effects on driving performance in these studies are solely attributable to differences in drug concentrations at the time of testing. Instead, the differences must be somehow related to the periods that elapsed between drug administration and performance testing.

Nocturnal doses of the sedating H_1 antagonist chlorpheniramine failed to affect driving performance of healthy volunteers when measured the next morning in the standard on-the-road driving test (Vermeeren *et al.*, 1998). These results could also not be explained by the drug concentrations at the time of testing, since chlorpheniramine possesses an elimination half-life of over 24 h. However, the use of a sustained release formulation appeared to contribute to the explanation of those results. Similarly, Ray *et al.* (1987) found no association between the use of sedating H_1 antagonsists for promoting sleep and the risk of hip-fracture in an epidemiological survey. In another study, designed to measure the effects of the H_1 antagonist diphenhydramine, performance was initially impaired, but then recovered completely after a 60 min nap (Roehrs *et al.*, 1993). These results seem to indicate that H_1 blockade specifically activates sleep mechanisms which in turn may be reversed by sleep. Mianserin and mirtazapine are also known to produce sedation by H_1 receptor antagonism. Yet, in the current study, sleep apparently mitigated the drugs' sedative effects on psychomotor and driving performance in a similar, but as yet unknown, manner.

Mianserin and mirtazapine had comparable effects on mood, subjective feelings and sleep. Decrements in alertness, contentedness and an increment in sleep duration could be measured throughout treatments with both drugs. Self-rated side-effects were maximal at the beginning of treatment and persisted over time. The magnitude of these side-effects were about the same for both drugs. Feelings of lethargy and drowsiness were pronounced in both drug treatments. These were accompanied by feelings of weakness, dry mouth and dizziness. Subjective feelings were more affected than objective performance, but this seems mainly due to the fact that the former were rated in the evening shortly after drug administration, and the latter were measured the next day. Spontaneously reported adverse effects were similar to side-effects just mentioned. During mirtazapine and mianserin treatment, adverse events that were reported most frequently were respectively: fatigue (11 and 17×), drowsiness (12 and 11×), dry mouth (4 and 6×), dizziness (3 and 6×) and difficulty

concentrating (3 and 4×). The only difference between drugs was the total number of complaints; i.e. 48 during mirtazapine and 69 during mianserin treatment.

Objective and subjective results all converge on the fact that both mirtzapine and mianserin are mildly sedating throughout 2 weeks of treatment. Apparently, both drugs' sedating effects on daytime performance are much alleviated by nocturnal administrating. Presumably, this is the reason why mirtazapine is currently recommended to be taken in single evening doses. Mianserin, on the other hand, is often prescribed as divided doses over the day. In our opinion, nocturnal dosing should be recommended for both drugs. This would not only promote their safety over days, it would also utilize their sleep-inducing properties for avoiding the occasional necessity for hypnotic coadministration.

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