HUMAN PSYCHOPHARMACOLOGY
Hum Psychopharmacol Clin Exp 2004; **19**: 1–7.
Published online in Wiley InterScience (www.interscience.wiley.com). **DOI**: 10.1002/hup.557

Double-blind comparative study of the action of repeated administration of milnacipran versus placebo on cognitive functions in healthy volunteers

M. F. Poirier[1], A. Galinowski[1], I. Amado[1], R. Longevialle[1], M. C. Bourdel[1], A. Tournoux[2]*, C. Serre[2] and H. Loo[1]

[1]*Service Hospitalo-Universitaire de Santé Mentale et de Thérapeutique, Centre Hospitalier Sainte-Anne, 1 rue Cabanis, 75014 Paris, France*
[2]*Pierre Fabre Médicament, 45, Place Abel Gance, 92654 Boulogne, France*

Objective The principal objective was to compare the effects of milnacipran, an antidepressant characterized by a dual-action on serotonin and noradrenaline reuptake, with placebo on memory, attention and psychomotor performance in healthy volunteers. The secondary objective was to evaluate the effects of milnacipran on mood, anxiety and vigilance in these subjects.
Methods In a double-blind crossover randomized trial, milnacipran (50 mg b.d.) or placebo was administered during two periods of 7 days separated by a washout period of 7 days. Memory tests (recall of words, images and coloured bars), tests to evaluate attention and vigilance (squares test, critical flicker fusion test and choice reaction time test) and visual analogue scales for affect and sleep were used.
Results There were no significant differences between milnacipran and placebo groups with respect to the psychomotor functions tested. No differences were observed in the Norris scales for vigilance, anxiety or satisfaction or in the sleep questionnaire (sleep latency, sleep quality and waking).
Conclusion Milnacipran, administered at 100 mg per day for 7 days to healthy volunteers, had no effects on cognitive functions.

KEY WORDS — milnacipran; placebo; cognition; volunteers; healthy

INTRODUCTION

Milnacipran is an antidepressant (Kasper *et al.*, 1996; Lecrubier *et al.*, 1996; Lopez-Ibor *et al.*, 1996; Montgomery *et al.*, 1996; Rouillon *et al.*, 2000a,b) characterized by an equipotent inhibition of the reuptake of serotonin and noradrenaline (Briley *et al.*, 1996). These properties have been demonstrated *in vitro* and *in vivo* (Moret *et al.*, 1985). The expected consequence of the inhibition of monoamine reuptake by milnacipran is an increase of synaptic levels of serotonin and noradrenaline (Moret and Briley, 1997) along with enhanced activation of one or more postsynaptic receptors thought to be necessary for a therapeutic antidepressant action. Milnacipran does not interact directly with any of 40 receptors tested (Moret *et al.*, 1985; and unpublished data). In particular, and in contrast to the tricyclic antidepressants (TCAs), milnacipran has no affinity for α_1-adrenoceptors, muscarinic or histaminergic H_1 receptors, which are thought to be responsible for the orthostatic hypotension, anticholinergic effects (dry mouth, constipation, blurred vision) and sedation seen with TCAs (Briley *et al.*, 1996).

It is well recognized that the depressed state impairs thought processes, in particular concentration and memory (Sobin and Sackheim, 1997). Certain antidepressants are known to further disturb thinking (O'Hanlon, 1996; Hindmarch, 1998). The undesirable

* Correspondence to: A. Tournoux, Pierre Fabre Médicament, 45, Place Abel Gance, 92654 Boulogne, France.
E-mail: alain.tournoux@pierre-fabre.com

Received 30 July 2003
Accepted 29 October 2003

action of these drugs on cognitive functions depends on the type of compound used, the subjects themselves (healthy volunteers or patients), dose and duration of administration and whether the condition is acute or chronic. In contrast to TCAs and other antidepressants, milnacipran has not demonstrated any sedation (Stenger *et al.*, 1987) in classical animal tests.

This study set out to compare the effects of milnacipran with placebo in terms of its effects on cognitive functions such as memory, attention and psychomotor performance in healthy volunteers.

PATIENTS AND METHODS

Ethics

The study was designed according to the principles of the Declaration of Helsinki and the French law of 20 December 1988 relating to clinical trials. Subjects received preliminary information on the objectives, methods and requirements of the trial and possible risks involved in the study. They were also informed of the characteristics of milnacipran and signed a declaration of well-informed consent. Subjects could withdraw from the study when they wanted. The protocol of the study was approved by the ethics committee of the Groupe Hospitalier Cochin, Saint Vincent de Paul and Sainte Anne in Paris.

Study design

The study was of single centre, double-blind, crossover design and took place in the Service Hospitalo-Universitaire de Santé Mentale et de Thérapeutique, Centre Hospitalier Sainte Anne, Paris. Subjects were randomly assigned to take either milnacipran or placebo for 7 days. Then, following a washout period of 7 days, subjects were crossed over for a further 7 days. Each 7-day sequence was preceded and followed by certain tests. The study enrolled 12 subjects, all of whom had one or more training sessions (day -7 to day -2) before the first treatment sequence.

Healthy volunteers of either sex, aged 20 to 35 years, having given their informed consent could be included in the study. A physical examination and an electrocardiogram (ECG) were given to confirm physical health. Subjects were required to have an IQ of at least 110, correct lateralization and a normal personality profile according to the Eysenck questionnaire (Eysenck and Eysenck, 1972). No major event must have occurred recently in their life according to the Paykel and Mangen questionnaire (Paykel *et al.*, 1971) which was completed before each sequence. No medical treatment was permitted during the 15 days previous to the study (except oral contraception) and during the whole study period. Tobacco consumption was permitted but alcohol was forbidden on the day preceding and the day of the tests.

The main exclusion criteria were participation in any therapeutic trial during the previous 6 months, personal or familial psychiatric history, psychotropic treatment (including benzodiazepines) during the previous month, alcoholism or drug addiction, somatic illness, allergy history, impairment of one of the principal organic functions, pregnancy or absence of efficacious contraception, biological anomalies.

After a preliminary evaluation session, milnacipran (100 mg daily dose) or placebo were administered orally twice daily at 09:00 and at 20:00 during meals. The treatment was changed during the second sequence (day 15 to day 21). A second evaluation session took place 12 h after the last tablet at the end of each treatment sequence. The two treatment sequences (milnacipran or placebo) were separated by a washout period of 7 days.

Any subjects that experienced gastrointestinal disorders were withdrawn from the study.

Memory tests

To test auditory memory the subjects listened to a list of 15 words read at a rate of one word every 3 s. Immediate memory was tested by asking the subjects to recall, immediately following the reading of the list, as many words as possible from the list within 1 min. Deferred memory was tested by asking the subjects to recall as many words as possible from the list within 1 min, 30 min after the reading of the list. Word recognition was evaluated by asking subjects to recognize words quoted in the initial list when included in a story. The number of correctly recalled words, the number of repetitions and the number of errors were recorded. The results are the means of five sequences of the above test.

Visual memory was evaluated by an image test based on that of Warot *et al.* (1989). Twelve images were presented to subjects at a rate of one image every 10 s. Immediate memory was tested by asking the subjects to recall as many images as possible during 2 min. Deferred memory was tested by recall of the images during 2 min, 30 min after the initial presentation. To test image recognition subjects were asked to recognise the original images from a collection of 24. The number of correctly recalled images, doubles and errors were recorded.

The coloured bars test described by Crocq *et al.* (1984) was used to evaluate immediate visual memory, the ability to concentrate and the capacity for retention. Ten bars were presented on a computer screen. Initially two of the bars were coloured (red or blue) for 7 s and then the colouring disappeared. The subject was required to indicate the position of the coloured bars and their colour following each presentation. The number of bars that were coloured increased as the test progressed. The score was established for a total of 36 presentations of increasing difficulty (greater number of coloured bars). The total duration of the trial and percent errors were recorded.

Attention and vigilance tests

Sustained attention was evaluated in an image recognition test based on that described by Crocq *et al.* (1984). Two geometric figures (a square and a hyphen) were permanently displayed at the top of a computer screen. Subjects were required to indicate the figures which corresponded to the reference models (in any orientation) from a series of 100 figures presented in random succession. The duration of the trial and percent of errors were measured.

The critical flicker fusion (CFF) test (as reviewed by Smith and Misiak, 1976; Fairweather *et al.*, 1995) evaluates the global level of vigilance and the reactivity of the central nervous system. The system used in this study consisted of four equidistant central red lights blinking at increasing frequency on a black computer screen, placed at 1 m from the subject. Subjects determined at which moment the frequency of the blink became a concentric fusion of the four lights. Two trials with increasing and decreasing frequency were performed without scoring. The following three trials were then scored. The final score represents the mean of the frequencies of fusion of these three trials.

Choice reaction time was measured using a group of six lamps. One lamp was illuminated at random and the subject was required to turn off this lamp by selecting the correct switch. The total reaction time took into account the decision time and the motor time. The mean reaction time was calculated from 50 repetitions of the test.

Evaluation scales

Subjective evaluation of psychomotor state and mood was determined using 18 visual analogue scales (10 cm horizontal lines) identified by pairs of bipolar adjectives describing different dimensions of mood, e.g. tense–relaxed, antagonistic–friendly based on those developed by Norris (1971) and modified by Herbert *et al.* (1976). The results were clustered into three groups representing vigilance, satisfaction and anxiety. Ten visual analogue scales, evaluating sleep latency, sleep quality and waking during the previous night, were adapted from the Leeds sleep questionnaire (Parrott and Hindmarch, 1980).

Testing sequence

In order to allow the subjects to become accustomed to the evaluation trials and to reach their best performance level, one or more learning sessions of the different psychomotor tests were held during the week before the trial (day −7 to day −2). The tests were then performed according to the following sequence:

- the day before the first treatment sequence (day 0)
- at the end of the first treatment sequence (day 8), the last dose having been administered the day before at 20:00
- at the beginning of the second treatment sequence (day 15)
- at the end of the second sequence (day 22)

The psychomotor tests were carried out in the following order:

1. Auditory recall test (five tests with recall during the following minute),
2. Image test (immediate recall during the following 2 min)
3. Coloured bars test
4. Sustained attention test
5. Auditory deferred word recall and recognition (in a story), (30 min after the first part)
6. Deferred recall of images and image recognition
7. Critical flicker fusion (CFF) test
8. Choice reaction time test.

Assessment of psychomotor state and mood, using the Norris visual analogue scales were carried out during inclusion and then during each session of tests (day 0, day 8, day 15, and day 22). The sleep questionnaire was carried out at inclusion and at the end of each treatment sequence (day 8 and day 22).

The personality questionnaire (Eysenck) was completed at inclusion. The questionnaire of Paykel *et al.* was completed at inclusion and also before each treatment sequence in order to verify the absence of any contraindication linked to life events.

Statistics

Initial inter-group homogeneity was verified by performing a variance analysis on the measurements

carried out before treatment. Intra-group evolution with milnacipran or placebo was calculated by analysis of variance of the differences before/after treatment. The effects of milnacipran and those of placebo were compared by an analysis of variance on the differences before/after treatment between the groups. To take into account the crossover, three factors were analysed: the sequence factor (or order factor), the period factor and the treatment factor. A statistical significance level of 5% was chosen. Data treatment and results analysis were carried out by the Computer and Statistical Department of the Centre conducting the study.

RESULTS

Twelve healthy subjects (six male, six female) aged 23 to 30 years were included in the study. Subjects were either doctors or pharmacists and all had an IQ greater than 110. The responses to the Eysenck and Paykel questionnaires showed that they had normal personality, and that no events classified as 'life disturbing' had recently taken place. Physical health evaluation and ECG were normal for all subjects. The responses to the sleep questionnaire showed that the mean duration of their sleep was at least 6 h. Somatic and psychiatric examinations were normal with no alcohol, toxic substances or drugs dependence.

Five of the six subjects in the group in which milnacipran was administered first were female, and five of the six subjects in the group in which placebo was administered first were male. One male and one female withdrew from the study because of vomiting reactions and a general sensation of discomfort after the first dose of milnacipran. Consequently the analysis was carried out on 10 subjects, 5 receiving milnacipran during the first sequence, and 5 receiving placebo during the first sequence.

In spite of randomization, the results of the image tests obtained at baseline (before drug administration) were better in the group that subsequently received milnacipran during the first week than in the other group ($p = 0.03$ for the immediate memory; $p = 0.008$ for the differed memory).

A period effect was found in three parameters: auditory test ($p = 0.03$ for the recognition), the test of coloured bars ($p = 0.01$ for the duration), the squares test ($p = 0.02$ for the duration). The results were significantly better and the durations shorter at day 15 than at day 1 independent of the treatment sequence. Because of this apparent learning effect differences between performances before and after each treatment were compared instead of using raw data.

Comparison of performances before and after administration of placebo showed a significant shortening of the duration in the coloured bars test ($p = 0.02$) and the squares test ($p = 0.03$). The evolution of the percentage of errors in these two tests was, however, not significant.

Comparison of results of tests before and after administration of milnacipran showed significant effects in three parameters with a shortened duration of the coloured bars test ($p = 0.04$), an improvement in the squares test ($p = 0.02$) and an increase in the threshold of the CFF test ($p = 0.009$). The deferred visual memory showed a tendency to improve ($p = 0.088$). No parameter was worsened by the administration of milnacipran.

Comparison between the observed changes with placebo or milnacipran

The comparisons were carried out on the differences of performances observed before and after the administration of placebo or milnacipran. Neither an order nor a period effect was detected under these conditions. Tables 1–3 summarize the results of memory tests, attention and vigilance tests and of the Norris scales.

No significant differences were observed between the values observed with milnacipran and placebo in the memory tests (auditory recall test, image test and coloured bars test) (Table1). However, a tendency was observed in the image test where the deferred visual memory improved with milnacipran compared with placebo ($p = 0.067$).

There was no significant difference between the values obtained with milnacipran and placebo for attention or vigilance (Table 2).

The 18 items included in the Norris visual analogue scales were grouped into three factors, F1 (vigilance), F2 (satisfaction), F3 (anxiety). There was no significant difference between the values obtained with milnacipran and placebo on the Norris visual analogue scales (Table 3).

Sleep questionnaire

The sleep questionnaire was used only at inclusion and at the end of each sequence (in contrast to the other parameters which were evaluated before and after each sequence). Therefore, the comparison was carried out only on the mean values observed after each treatment sequence and not on the differences before/after treatment. The existence of a sequence and a period effect were investigated. A significant

Table 1. Comparison of the effects of milnacipran and placebo on memory tests

	Placebo ($n=10$)		Milnacipran ($n=10$)		
	D0	Δ after treatment	D0	Δ after treatment	Statistical significance
Auditory test					
Immediate	14.8 ± 0.4	0.20 ± 0.42	14.8 ± 0.6	0.20 ± 0.63	$p=1.0$
Differed	14.5 ± 1.3	0.50 ± 1.27	14.3 ± 1.2	0.70 ± 1.25	$p=0.59$
Recognition	14.3 ± 0.8	0.50 ± 0.97	14.5 ± 0.8	0.40 ± 0.97	$p=0.72$
Images test					
Immediate	11.7 ± 0.7	-0.20 ± 0.42	11.3 ± 0.8	-0.10 ± 1.10	$p=0.79$
Differed	11.0 ± 1.6	-0.20 ± 1.13	10.5 ± 1.3	0.70 ± 1.16	$p=0.067$
Recognition	11.7 ± 0.5	0.30 ± 0.48	11.8 ± 0.4	0.00 ± 0.47	$p=0.19$
Coloured bars test					
Duration	109.6 ± 29.7	-7.26 ± 8.66	113.2 ± 17.5	-11.35 ± 15.07	$p=0.46$
% of errors	3.3 ± 4.7	-0.57 ± 5.03	6.1 ± 7.2	-2.78 ± 9.08	$p=0.53$

Values are mean ±SD. D0 are the values before treatment. Δ are the mean differences between the values after treatment and D0. The significance level refers to the comparison between the two groups (treatment effect).

Table 2. Comparison of the effects of milnacipran and placebo on attention and vigilance tests

	Placebo ($n=10$)		Milnacipran ($n=10$)		
	D0	Δ after treatment	D0	Δ after treatment	Statistical significance
Squares test					
Duration	26.3 ± 3.9	-2.81 ± 3.58	28.3 ± 5.0	-4.01 ± 4.51	$p=0.51$
% of errors	3.6 ± 2.4	5.20 ± 8.68	5.7 ± 7.5	-0.20 ± 10.0	$p=0.12$
CFF					
Final score	30.7 ± 2.9	0.65 ± 2.13	29.7 ± 1.9	1.66 ± 1.62	$p=0.26$
Reaction time					
Total	475 ± 65	-10 ± 29	465 ± 1.9	1 ± 25	$p=0.27$
Decision	340 ± 43	-5 ± 17	335 ± 48	-1 ± 18	$p=0.51$
Motor	135 ± 4	-4 ± 25	130 ± 33	2 ± 13	$p=0.45$

Values are mean ±SD. D0 are the values before treatment. Δ are the mean differences between the values after treatment and D0. The significance level refers to the comparison between the two groups (treatment effect).

Table 3. Comparison of the effects of milnacipran and placebo on the visual scales of Norris

	Placebo ($n=10$)		Milnacipran ($n=10$)		
	D0	Δ after treatment	D0	Δ after treatment	Statistical significance
Norris scales					
F1 alertness	23.4 ± 1.7	0.80 ± 1.2	23.6 ± 1.4	-0.28 ± 1.99	$p=0.19$
F2 mood	13.1 ± 1.4	0.31 ± 0.51	13.4 ± 0.9	-0.12 ± 0.57	$p=0.12$
F3 anxiety	5.8 ± 0.6	-0.11 ± 0.45	5.7 ± 0.3	0.02 ± 0.29	$p=0.51$

Values are mean ±SD. D0 are the values before treatment. Δ are the mean differences between the values after treatment and D0. The significance level refers to the comparison between the two groups (treatment effect).

period effect ($p=0.03$) was only observed on one of the 18 items (sleep—troubled/quiet). There was no significant difference between the mean values obtained after treatment with milnacipran and placebo on any of the items of the sleep questionnaire (Table 4).

Tolerance

Vomiting with a sensation of discomfort was the only side effect observed after the first dose of milnacipran. This led to the withdrawal of two subjects from the study.

Table 4. Comparison of the effects of milnacipran and placebo on the sleep questionnaire

Sleep questionnaire	Placebo ($n = 10$)	Milnacipran ($n = 10$)	Statistical significance
Falling asleep—difficult/easy	5.56 ± 0.44	4.76 ± 1.46	$p = 0.15$
Falling asleep—slow/rapid	5.32 ± 0.40	4.97 ± 1.66	$p = 0.50$
Drowsiness—absent/important	5.33 ± 0.45	5.04 ± 1.50	$p = 0.57$
Sleep—troubled/quiet	5.26 ± 0.29	5.13 ± 0.66	$p = 0.48$
Awakenings—many/rare	5.20 ± 0.38	4.76 ± 1.32	$p = 0.33$
Awakening—difficult/easy	5.48 ± 0.38	5.95 ± 1.76	$p = 0.47$
Awakening—rapid/slow	5.02 ± 0.29	5.40 ± 1.66	$p = 0.52$
Sensation of fatigue/well being after waking	4.77 ± 1.56	5.19 ± 2.02	$p = 0.66$
Sensation of fatigue/well being on getting up	5.28 ± 2.03	5.76 ± 2.09	$p = 0.68$
Equilibrium—unstable/stable	5.26 ± 0.40	5.46 ± 0.51	$p = 0.32$

Values are mean $\pm$ SD after treatment. The significance level refers to the comparison between the two groups (treatment effect).

DISCUSSION

The aim of the present study was to compare the action of milnacipran on cognition with that of placebo in healthy volunteers. Administered for 7 days to ten healthy volunteers at a daily dose of 50 mg b.d. milnacipran did not modify cognitive functions, particularly memory, attention or psychomotor performance. The principal evaluation criteria such as immediate and deferred auditory memory, immediate visual memory, sustained attention capacity, global level of awakening, central nervous system reactivity and sensory-motor performances showed no change following 1 week's treatment with milnacipran. It is noteworthy that the deferred visual memory tended to be improved with milnacipran compared with placebo. Similarly, the secondary evaluation criteria showed that the administration of milnacipran did not lead to any changes on vigilance, anxiety or level of satisfaction or quality of sleep, particularly sleep latency, the sleep itself or awakening.

In contrast to this absence of effects on cognition with milnacipran, many antidepressants, especially the TCAs do disrupt cognitive function (O'Hanlon, 1996; Hindmarch, 1998). A study comparing the TCA, amitriptyline, with a selective noradrenaline reuptake inhibitor, reboxetine, showed that amitriptyline lowered the critical flicker fusion (CFF) threshold and increased the reaction time and tracking error and slowed short-term memory scanning (Kerr *et al.*, 1996), while reboxetine had little or no effect on performance. Other studies comparing reboxetine and various antidepressants have shown that TCA agents are associated with an increased risk of accidents, especially in the elderly, in contrast to reboxetine which demonstrated improvements in the incidence and severity of effects on psychomotor function (Hindmarch, 1997). A test battery including choice reaction time, tracking, critical flicker fusion threshold and memory scanning was used to compare dothiepin and fluvoxamine in healthy male volunteers (Fairweather *et al.*, 1996). Dothiepin impaired performance in the majority of the tests and reduced daytime activity, whereas fluvoxamine did not impair psychomotor performance or cognitive ability in any of the tests (Fairweather *et al.*, 1996). Fairweather *et al.* (1993) found that the reversible monoamine oxidase inhibitor, moclobemide, increased reaction time in the tracking task but did not impair psychomotor performance or cognitive ability in any of the other tests. These data support the view that, whereas TCAs have a major negative impact on cognitive performance, more recent antidepressants such as the SSRIs, the selective noradrenaline reuptake inhibitors and the dual action reuptake inhibitor, milnacipran, respect the cognitive function.

These results observed following repeated administration of milnacipran in healthy, young, adult volunteers are consistent with those of Hindmarch *et al.* (2000) who reported that a single administration of milnacipran had no effect on the global level of awakening nor on the reactivity of the central nervous system.

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