HUMAN PSYCHOPHARMACOLOGY, VOL. 4, 221–227 (1989)

Controlled Comparison of Milnacipran (F2207) 200 mg and Amitriptyline in Endogenous Depressive Inpatients

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A multicentre study compared the antidepressant efficacy and the tolerance of milnacipran (200 mg/d) and amitriptyline (150 mg/d) in two parallel groups of 43 major depressive inpatients, endogenous subtype, as defined by Research Diagnostic Criteria. The duration of the study was 4 weeks, with weekly assessments by means of the Montgomery and Asberg depression scale (MADS), the Hamilton depression scale, the Clinical Global Impressions (CGI) and a checklist of symptoms and side-effects. Results showed similar improvement in both groups but better tolerance with milnacipran (less drowsiness and anticholinergic side-effects), reflected in the better scores on the therapeutic index of the CGI. The clinical profile of the two drugs was somewhat different with more transitory sedation with amitriptyline and more improvement in concentration difficulties with milnacipran during the first weeks of the study associated with more effect on retardation with milnacipran at the end of the study.

KEY WORDS—Milnacipran, midalcipran, F2207, antidepressant, amitriptyline, major depression, endogenous depression.

INTRODUCTION

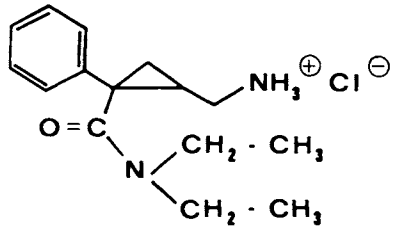

Figure 1. Structural formula of milnacipran (F2207)

Milnacipran (previously midalcipran or 1-phenyl-1-diethyl-amino-carbonyl-2-amino-methylcyclopropane hydrochloride) is a new potential antidepressant selected for its equipotent inhibition of noradrenaline and serotonin uptake and its lack of effect at any postsynaptic receptor (Moret *et al.*, 1985; Stenger *et al.*, 1987). Its biochemical and pharmacological profile suggested that milnacipran might be a potent antidepressant devoid of anticholinergic side-effects. Indeed, the activity on both the noradrenergic and serotonergic systems has been recently suggested to improve the antidepressant action (Van Praag, 1984). An open pilot study on 27 major depressed patients has shown that milnacipran (100 mg daily) had a significant antidepressant effect within 7 days; in addition, the drug was well tolerated without anticholinergic side-effects (Serre *et al.*, 1986).

We recently compared milnacipran 100 and 50 mg/d and amitriptyline 150 mg/d in three parallel groups of major depressive inpatients and found a statistically significant superiority of both milnacipran 100 mg/d and amitriptyline over milnacipran 50 mg/d after 4 weeks of treatment (Ansseau *et al.*, 1989). However, the latency of the clinical improvement was somewhat longer with milnacipran than with amitriptyline, with non-significant trend favouring amitriptyline after 2 weeks of treatment. We felt that this slower efficacy, partially related to the anxiolytic and sedative properties of amitriptyline, could also be due to a too low dose of milnacipran used in this study

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0885-6222/89/030221-07$05.00

Accepted 1 May 1989

performed in severely depressed inpatients. Therefore, the purpose of the present study was to test if a higher dose of milnacipran (200 mg/d) could yield some benefit in comparison to the standard reference drug.

SUBJECTS AND METHOD

Design of the study

The study was performed between February and August 1988 in eight Belgian centres frequently collaborating together in multicentre studies (see affiliations). The trial used a double-blind design with two parallel groups of patients randomly assigned to milnacipran 200 mg/d or amitriptyline 150 mg/d. The daily dose was progressively increased from day 1 to day 5: respectively 50, 100, 150, and 200 mg in the milnacipran group; and 50, 75, 100, 125, and 150 mg in the amitriptyline group. This incremental increase was designed to limit the side-effects of amitriptyline. The treatment was administered twice daily, morning and evening. The drug administration period was preceded by a wash-out period of 4–7 days on placebo and lorazepam (up to 10 mg/d) and nitrazepam (up to 5 mg/d) if needed. These associated drugs could be maintained during the treatment period if necessary. Benzodiazepines are frequently associated with antidepressants among depressive inpatients and were used so as not to modify the habits of some clinicians. The duration of the study was 4 weeks, with weekly assessments.

Subjects

A total of 87 inpatients were included in the study, two of which were not included in the statistical analysis for early drop-out (before day 14). Both patients received amitriptyline and left the study for, respectively, paranoid delusions and urinary retention. Therefore, the milnacipran group comprised 44 patients and the amitriptyline group 43 patients. Patients comprised 34 males and 53 females, aged from 23 to 68 years, with a mean age (SD) of 49·6 (11·6) years. All subjects were severely depressed inpatients who fulfilled Research Diagnostic Criteria (RDC) for a definite major depressive disorder, endogenous subtype (Spitzer *et al.*, 1978) and had a score of at least 25 on the Montgomery and Asberg depression scale (MADS) (Montgomery and Asberg, 1979), a score of at least 5 (markedly ill) for the severity of illness as defined by the Clinical Global Impressions (CGI) (Guy, 1976), and a score on the Raskin scale for depression higher than the score on the Covi scale for anxiety (Raskin *et al.*, 1967; Covi *et al.*, 1979). Initial scores ranged from 25 to 57 with a mean (SD) of 40·1 (6·6) on the MADS and from 25 to 54 with a mean (SD) of 37·5 (6·6) on the Hamilton depression scale. Patients presenting any evidence of contraindication for a tricyclic antidepressant, or serious or uncontrolled medical illness, were excluded from the study. The characteristics of the patients according to RDC subtypes of major depression are presented in Table 1. No statistically significant differences existed between the treatment groups.

Table 1. Frequency of RDC subtypes of major depression (percentages)

	Milnacipran group (n=44)	Amitriptyline group (n=43)
Primary/secondary	81·8/19·2	88·3/11·7
Recurrent	74·9	83·7
Psychotic	9·2	11·5
Incapacitating	95·4	95·4
Endogenous	100	100
Agitated	20·1	20·9
Retarded	79·6	83·8
Situational	27·3	18·6
Predominant mood		
Mainly depressed	70·4	76·8
Mainly apathetic	27·3	20·9
Other	2·3	2·3

All patients remained hospitalized for at least the first 2 weeks of treatment. Finally, the protocol was approved by the Ethical Committee of the University of Liège Medical School, and all patients were fully informed of the purpose of the study and gave their consent.

Assessments

Weekly assessments were performed by means of the MADS, the 24-item Hamilton depression scale (Hamilton, 1960; Guy, 1976), the CGI, and a checklist of symptoms and side-effects which comprises specific items as well as reserve items related to behaviour, central nervous system, autonomic nervous system and miscellaneous rated as 0 (none), 1 (mild), 2 (moderate), and 3 (severe) (see Table 3). Pulse and blood pressure in the supine and standing positions were measured weekly. An ECG

was performed before treatment and 2 weeks later, whereas laboratory tests, including hepatic and renal balance sheets, were carried out before treatment and at the end of the treatment period.

Data analysis

Initially the homogeneity of the two treatment groups was controlled, using an analysis of variance (ANOVA) or chi-square statistics, eventually corrected by the Yates test for small samples. No significant differences were present related to age, weight, height, gender, civil status distribution, the three scores on the Raskin and Covi scales, scores on the MADS and the Hamilton scale, frequency of RDC subtypes of major depression, previous psychotropic treatments, and personal and family psychiatric history. However, the eight centres differed in the baseline severity of depressive symptomatology, as measured by the MADS and the Hamilton scale ($F(6,73) = 8{\cdot}04$, $p < 0{\cdot}0001$ for the MADS and $F(6,73) = 4{\cdot}10$, $p = 0{\cdot}001$ for the Hamilton scale), and the changes over time in depressive symptomatology were analysed as percentage of improvement related to the baseline scores. This difference in severity of depression depends mainly on the type of psychiatric department (university hospital, general hospital, or psychiatric hospital) which recruits different types of patients, both socially and clinically.

All changes over time in ratings were assessed by ANOVAs with repeated measures. A second analysis was also performed reporting the endpoint scores for subsequent evaluations of patients who did not complete the 4-week protocol, but since the conclusions were similar they are not reported in this paper. All ANOVAs with repeated measures were followed by time-by-time ANOVAs associated with Bonferroni tests in order to complete the comparison between groups at intermediate times. All statistical procedures used a SAS package.

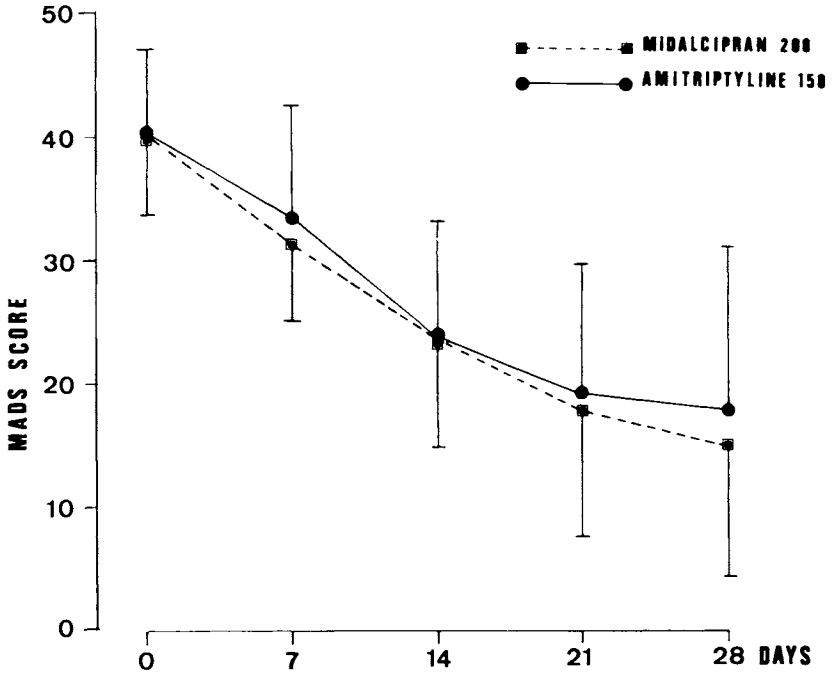

Figure 2. Changes over time in mean scores (±SD) on the MADS among patients treated by milnacipran 200 mg/d or amitriptyline 150 mg/d.

Table 2. Comparison of efficacy between milnacipran and amitriptyline (mean and SD)

	Day 0	Day 7	Day 14	Day 21	Day 28	$F(3,75)$	p
MADS							
Milnacipran	40·1 (6·3)	31·4 (6·3)	23·6 (8·7)	17·9 (10·2)	15·0 (10·7)	1·06	NS
Amitriptyline	40.2 (6·9)	33·6 (9·0)	23·7 (9·5)	19·2 (10·6)	18·0 (13·3)		
Hamilton depression scale							
Milnacipran	37·3 (6·3)	29·8 (6·8)	22·0 (8·4)	17·7 (10·0)	14·1 (10·0)	2·01	NS
Amitriptyline	37·6 (7·0)	30·3 (8·9)	21·5 (8·9)	17·5 (9·5)	16·7 (12·4)		
CGI-1							
Milnacipran	4·75 (0·7)	4·27 (0·8)	3·45 (1·0)	2·60 (1·4)	2·07 (1·5)	1·68	NS
Amitriptyline	4·88 (0·7)	4·33 (0·9)	3·44 (1·1)	2·85 (1·4)	1·66 (1·5)		
CGI-2							
Milnacipran	—	2·18 (0·8)	1·61 (0·9)	1·21 (1·2)	1·00 (1·3)	1·23	NS
Amitriptyline	—	2·36 (0·8)	1·47 (0·8)	1·15 (0·9)	1·16 (1·2)		
CGI-3							
Milnacipran	—	1·50 (0·7)	1·87 (0·9)	2·22 (1·2)	2·53 (1·3)	4·34	0·04
Amitriptyline	—	1·18 (0·5)	1·61 (0·7)	1·82 (1·0)	1·89 (1·1)		

RESULTS

Drop-outs

A total of six patients (6·9 per cent) left the study between day 14 and day 28 for side-effects: three (6·8 per cent) in the milnacipran group and three (7·0 per cent) in the amitriptyline group. Reasons for these drop-outs were as follows: worsening of mictional difficulties (discontinuation at day 14), severe constipation (discontinuation at day 21), and nausea with vomiting (discontinuation at day 23) in the milnacipran group; daytime drowsiness (discontinuation at day 14), orthostatic hypotension (discontinuation at day 21), and hypomania with delusions (discontinuation at day 21) in the amitriptyline group.

MADS

The changes over time on the MADS in the two groups are presented in Table 2 and Figure 2. No significant differences were present. The analysis of individual items of the MADS revealed one difference favouring amitriptyline: reduced sleep (p = 0·02 at day 14) and one difference favouring milnacipran: concentration difficulty (p =0· 03 from day 7 to day 21).

Hamilton depression scale

The changes over time on the Hamilton depression scale in the two treatment groups are presented in Table 2 and Figure 3. No significant differences between drugs were present. Changes over time in individual item scores revealed one difference favouring milnacipran: retardation (p = 0·01 from day 7 to day 28) and one difference favouring amitriptyline: late insomnia (p = 0·003 at day 7).

CGI

The CGI-1, related to the severity of illness, did not exhibit significant differences between the two treatment groups. The results of the CGI-2, related to the global improvement, were similar. In contrast, the CGI-3, related to the efficacy index, exhibited differences favouring milnacipran with better therapeutic indexes at day 7 (p = 0·04) and day 28 (p □ 0·02) (Figure 4).

Side-effects

The comparison of the frequency of side-effects in the two treatment groups is presented in Table 3. Three side-effects were more frequently reported with amitriptyline: drowsiness, dryness of the mouth, and blurred vision. Blood pressure, pulse

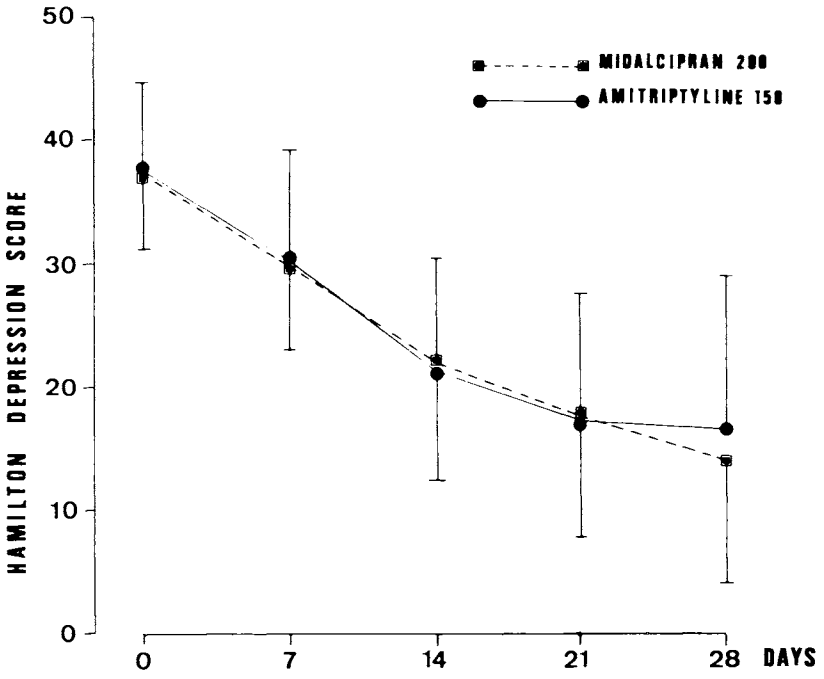

Figure 3. Changes over time in mean scores (±SD) on the Hamilton depression scale among patients treated by milnacipran 200 mg/d or amitriptyline 150 mg/d.

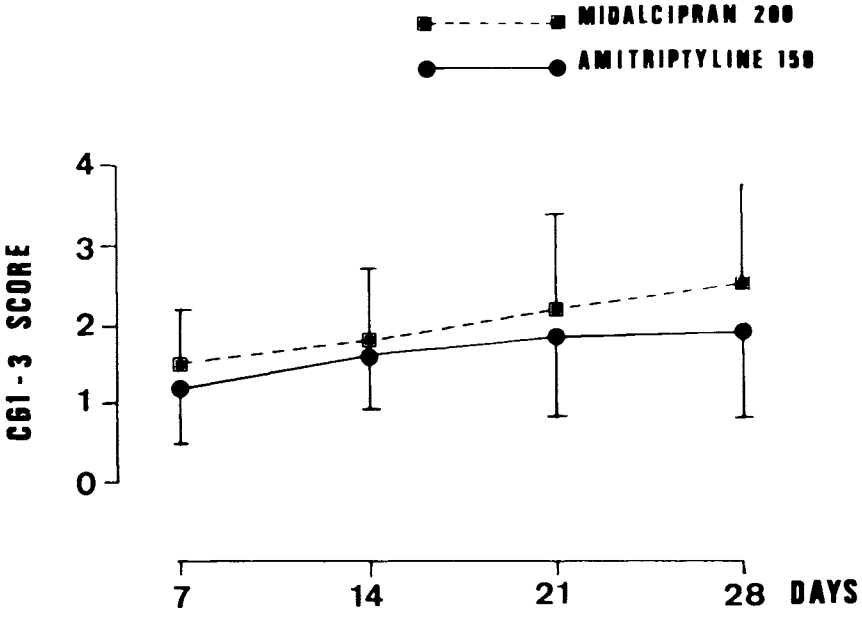

Figure 4. Changes over time in mean scores (±SD) on the CGI related to efficacy index among patients treated by milnacipran 200 mg/d or amitriptyline 150 mg/d.

Table 3. Comparison of the frequency (percentages) of side-effects with Milnacipran and Amitriptyline

	Milnacipran group (n=44)	Amitriptyline group (n=43)	p
Adverse behaviour effects			
Insomnia	6·8	4·6	NS
Drowsiness	4·5	39·5	0·0001
Excitement–nervousness	15·9	23·3	NS
Depression	2·3	—	NS
Confusion	—	4·6	NS
Central nervous system			
Rigidity	—	—	NS
Tremor	22·7	9·3	NS
Dystonic symptoms	2·3	2·3	NS
Akathisia	6·8	—	NS
Autonomic nervous system			
Hypotension	13·6	27·9	NS
Syncope	2·3	9·3	NS
Tachycardia–palpitations	25	18·6	NS
Nasal congestion	2·3	6·9	NS
Dry mouth	34·1	62·8	0·007
Increased salivation	2·3	—	NS
Blurred vision	11·4	32·6	0·02
Nausea or vomiting	22·7	11·6	NS
Diarrhoea	6·8	—	NS
Constipation	29·5	34·9	NS
Miscellaneous			
Dermatitis–allergy	2·3	—	NS
Headache	20·4	20·9	NS
Lightheadedness, dizziness, faintness, weakness	25	25·6	NS
Weight gain, excessive	9·1	11·6	NS
Weight loss, excessive	13·6	9·3	NS

rate, and weight did not exhibit any significant changes over time, or differences between treatment groups. Finally, no significant alteration in the ECGs and in the laboratory tests were noted in any of the treatment groups.

Associated anxiolytic and hypnotic benzodiazepines

The mean daily intake of lorazepam was higher with milnacipran than with amitriptyline at day 7 (3·3 mg vs 2·1 mg, $F(1,85) = 3·56$, $p = 0·07$, trend), at day 14 (3·3 mg vs 1·8 mg, $F(1,83) = 6·00$, $p = 0·02$), and day 21 (3·1 mg vs 1·5 mg, $F(1,82) = 7·39$, $p = 0·01$). In fact, the intake of lorazepam was already somewhat higher in the milnacipran group at inclusion (3·3 mg vs 2·5 mg) and no increase of lorazepam existed during the treatment with milnacipran but the decrease of lorazepam was more rapid during the treatment with amitriptyline.

No difference existed in the associated intake of nitrazepam: 2·4 mg at day 0 and 2·3 mg at day 28 with milnacipran and 2·0 mg at day 0 and 1·6 mg at day 28 with amitriptyline.

DISCUSSION

The results of the present study show similar efficacy of milnacipran 200 mg/d and amitriptyline 150 mg/d. In contrast to our previous study comparing milnacipran 50 mg/d, 100 mg/d and amitriptyline 150 mg/d, the present study does not show any difference in the latency of the clinical improvement between milnacipran 200 mg/d and amitriptyline 150 mg/d. These results suggest a relationship between dose and onset of action for milnacipran, and that a dose of 200 mg is necessary in endogenous depressive inpatients. The selection of the 100 mg daily dose for milnacipran in the previous study was essentially based on an open pilot study in 27 major depressive inpatients which showed excellent or good results in 68 per cent of the patients (Serre *et al.*, 1986). In this study the initial dose of milnacipran was 100 mg daily, and could be doubled after 2 weeks. Ten patients were then treated with 200 mg/d while 17 patients remained at the 100 mg daily dose. The comparison of outcome between these two subgroups did not appear to confer special benefit.

The clinical profile of milnacipran and amitriptyline seems somewhat different, with better activity of amitriptyline on sleep disorders and better activity of milnacipran on concentration difficulties and retardation. The sedative properties of amitriptyline are well known (Enelow, 1975) and may relate more to side-effects than to a true antidepressant activity. It should be noted that this difference is transitory (from day 7 to day 14), and that milnacipran also improves insomnia but with a somewhat longer latency which seems more related to the antidepressant effect. The higher rate of daytime sedation induced by amitriptyline may support this hypothesis. Moreover, the decrease in associated lorazepam is more rapid in the amitriptyline group. The low rate of sedative side-effects observed with milnacipran may result from the lack of affinity of the compound for alpha-1-noradren-

ergic and histamine-H-1-receptors which contrasts to amitriptyline (Moret *et al.*, 1985).

The only difference in the changes over time in symptom severity which remains significant at the end of the treatment period favours milnacipran: the effect on retardation. The transitory better clinical efficacy of milnacipran on concentration difficulties may result from its lack of anticholinergic properties (Moret *et al.*, 1985; Stenger *et al.*, 1987). In this regard, milnacipran could be safer to use in elderly depressive patients than standard tricyclics.

The limitation of the study period to 4 weeks may be criticized. Indeed, the endpoints in rating scales indicate that the patients were still significantly depressed at the end of 4 weeks and that 1 or 2 more weeks of study would have improved the treatment response, particularly in the milnacipran group, where the improvement between the third and the fourth week of treatment was more apparent than in the amitriptyline group.

Milnacipran is responsible for significantly less anticholinergic side-effects (dryness of the mouth and blurred vision) than amitriptyline. These results confirm the lack of affinity of milnacipran for muscarinic receptors (Moret *et al.*, 1985) as well as its lack of affinity in animal tests showing an interaction with the cholinergic system (Stenger *et al.*, 1987).

Digestive side-effects, such as nausea and vomiting, were reported no more frequently with milnacipran than with amitriptyline. This is particularly interesting since most recent antidepressants, such as viloxazine, trazodone, fluvoxamine, or fluoxetine, induce fewer anticholinergic side-effects than standard tricyclics but more digestive side-effects (Feighner, 1986). The overall lower rate of side-effects of milnacipran may explain why it obtains significantly better scores than amitriptyline on the therapeutic index of the CGI, which takes into account both efficacy and tolerance of the treatments.

In conclusion, this study shows similar antidepressant efficacy of milnacipran 200 mg and amitriptyline 150 mg/d but better tolerance of milnacipran. It confirms that a daily dose of 200 mg of milnacipran may be necessary among severely depressed inpatients. The excellent tolerance of milnacipran might be an argument to test if higher doses might improve its therapeutic results.

ACKNOWLEDGEMENTS

The authors would like to thank Drs M. A. Gerard-Vandenhove, M. Michaux, and P. Kremer, who participated in the study; M. von Frenckell-Spiertz, who coordinated the data collection; and Ch. Gayetot, who typed the manuscript.

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