Published in : International Clinical Psychopharmacology (1998), vol. 13, n°3, pp. 121–128
DOI:10.1097/00004850-199805000-00005
Status : Postprint (Author's version)

A DOUBLE-BLIND OF THE EFFICACY AND SAFETY OF MILNACIPRAN AND FLUOXETINE IN DEPRESSED INPATIENTS

J.D. Guelfi[a], M. Ansseau[b], E. Corruble[a], J.C. Samuelian[c], I.Tonelli[d], A. Tournoux[d], Y. Plétan[d]

[a]*University Paris XI, Department of Psychiatry, Hôpital Paul Brousse, Villejuif, France ;*
[b]*Department of Psychatry, CHU du Sart Tilman, Liège, Belgium ;*
[c]*Department of Psychiatry, CHU La Timone, Marseille ;*
[d]*Institut de Recherche Pierre Fabre, Boulogne, France.*

KEYWORDS: antidepressant, efficay, fluoxetine, depression, milnacipran

ABSTRACT

This double-blind, randomised, multicentre study compared the antidepressant efficacy and safety of two doses of milnacipran (100 mg/day and 200 mg/day) and fluoxetine (20 mg/day) in 289 inpatients with endogenous depression. After a placebo washout period of 4-7 days, assessments were performed weekly during the first 4 weeks, and then after 6, 8 and 12 weeks, using the 17-item Hamilton Depression Rating Scale (HDRS), the Montgomery - Asberg Depression Rating Scale (MADRS) and the Clinical Global Impression (CGI). HDRS total score was reduced by a mean of 14.8 in the milnacipran 100 mg/day group, 12.9 in the milnacipran 200 mg/day group and 12.1 in the fluoxetine 20 mg/day group. MADRS total score decreased by 17.4, 15.8 and 14.6, respectively. No significant difference could be shown between the three treatment groups for either the HDRS or MADRS total scores. However, the time-by-time change showed a trend in favour of milnacipran 100 mg/day, which was found significantly superior to fluoxetine at day 28 for several converging parameters (MADRS, CGI-3). Overall, efficacy ratings for all parameters were highest for milnacipran 100 mg/day, followed by milnacipran 200 mg/day and fluoxetine 20 mg/day. Side-effect profiles were not significantly different between groups except for a significantly greater frequency of dose-related increase in heart rate ≥100 bpm in milnacipran recipients and a significantly greater weight loss in fluoxetine recipients.

Published in : International Clinical Psychopharmacology (1998), vol. 13, n°3, pp. 121–128
DOI:10.1097/00004850-199805000-00005
Status : Postprint (Author's version)

Introduction

Milnacipran, a non-trycyclic cyclopropane, is a new antidepressant which selective inhibits the reuptake of serotonin and noradredaline without any direct effect at any postsynaptic receptor site (Moret *et al.*, 1985). Milnacipran is active in behavioural tests of noradrenergic and serotonergic function and has also shown efficacy in animal models of depression (Stenger *et al.*, 1987; Redmond *et al.*, 1995). Human pharmacokinetic studies have revealed an 8 h plasma half-life and the absence of active metabolites (Puozzo and Leonard, 1996).

Clinical studies of milnacipran have included more than 4000 patients treated with this agent. Among 31 double-blind trials performed in hospitalized or ambulatory patients with major depressive disorder, 14 compared the effects of milnacipran 100 mg/day with those of placebo (three studies), trycyclic antidepressants (TCAs; nine studies) and selective serotonin reuptake inhibitors (SSRI; two studies) (Kasper *et al.*, 1996; López-Ibor *et al.*, 1996).

Milnacipran has been shown to be effective in major depressive episodes (adults and the elderly) at a dosage of 100 mg/day, i.e. two 50 mg capsules given with meals morning and evening. At this dosage, milnacipran has been shown to be superior to placebo (Lecrubier *et al.*, 1996) and as efficacious as TCAs. In nine comparative trials versus TCAs, milnacipran was found equivalent as in one Clerc's study (1990) with the exception of one trial where clomipramine was found superior (Kasper *et al.*, 1996). Previous studies comparing milnacipran 1OO or 200 mg/day with SSRis have included three trials with fluvoxamine (Lôpez- Ibor *et al.*, 1996) and one with fluoxetine (Ansseau *et al.*, 1994).

In the two trials comparing milnacipran and fluvoxamine (200 mg/day), the daily doses of milnacipran ranged between 200 and 300 mg, and no differences between treatments were found (Ansseau *et al.*, 1991). Nevertheless, it was later shown clearly that these high doses of milnacipran were less effective than the 100 mg dose (unpublished data, Institut de Recherche, Pierre Fabre). Hence, the third study compared milnacipran 100 mg/day with fluvoxamine 200 mg/day in a sample of 113 patients over a 6-week period (López-lbor *et al.*, 1996). Although the difference in HDRS score at end-point was not statistically significant between treatments, there was a lack of statistical power and therefore the magnitude of the difference, in favour of milnacipran, was deemed interesting in clinical terms (Δ HDRS = 2.9 points, difference in response rate on HDRS = + 16%). The only study comparing milnacipran with fluoxetine 20 mg/day (including 190 patients treated for 6 weeks) demonstrated an advantage for fluoxetine (Δ MADRS = 3.4 points, difference in response rate on MADRS = 22%) (Ansseau et *al.*, 1994). However, in this study milnacipran 100 mg was administered once daily, and it has been shown subsequently that a once-daily regimen is inadequate because milnacipran has a relatively short half-life ($t_{1/2}$ = 8 h) and no active metabolite (Puozzo and Leonard, 1996). In a separate study, twice-daily administration yielded a 20% difference in HDRS response rate compared with once-daily administration in the morning (Institut de Recherche, Pierre Fabre, unpublished data).

In view of the design of the present study, this is the first fair comparison of milnacipran and fluoxetine because both drugs were administered according to the usual recommended dosage regimen.

Published in : International Clinical Psychopharmacology (1998), vol. 13, n°3, pp. 121–128
DOI:10.1097/00004850-199805000-00005
Status : Postprint (Author's version)

Methods

This multicentre, randomized double-blind study was concluded by 60 centres (47 in France, 13 in Belgium). The number of investigators was between one and six per centre. The number of patients per centre was between one and 26. After a 4- to 7-day placebo washout period, patients were randomized in three parallel groups receiving milnacipran 100mg/day (50 mg in the morning and in the evening; $n = 100$ patients), milnacipran 200 mg/day (100 mg in the morning and in the evening n = 100) or fluoxetine 200 mg/day (20 mg in the morning and placebo in the evening; n = 100) in a double-blind manner for 12 weeks. Assessments were performed weekly during the first 4 weeks, and subsequently, after 6, 8 and 12 weeks.

The 289 inpatients (95 men and 194 women aged 18-70 years) included in the study fulfilled DSM III-R criteria for major depression (American Psychiatric Association, 1987). All patients had been depressed for less than 3 months, had a minimum score of 22 on the 17-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) at the end of the washout period, and fulfilled endogenous criteria according to the Newcastle Scale (score ≥ 6) (Roth *et al.*, 1983) or to HDRS specific endogenous subscore (score ≥ 8) (Thase *et al.*, 1983). Patients were moderately to extremely ill according to the first item of the Clinical Global Impression (CGI) (Guy, 1976). Exclusion criteria were : serious or uncontrolled medical illness; no remission between episodes; depression with psychotic features, dysthymia; personality disorders; lack of response to two antidepressants; patients requiring electroconvulsive therapy or neuroleptics; major risk of suicide; schizophrenia and dependence on psychoactive substances (DSM III-R) during the previous 6 months; treatment with monoamine oxidase (MAO)-inhibitors in the 2 weeks before inclusion; administration of fluoxetine or thymoregulators in th 4 weeks before inclusion; long-active neuroleptics or electroconvulsive therapy in the 3months before inclusion; pregnancy, lactation and lack of contraception in non-menopausal women. All patients were fully informed and provided written informed consent (approval was obtained from the Ethical Review Comittees of Paris, Cochin and Liège). All patients were hospitalized for the first 2 weeks of treatment.

COMEDICATION

Psychotropic drugs were not allowed, except oxazepam in daily doses ≤ 50 mg/day or chloral hydrate in daily doses < 2g/day in case of anxiety and/or insomnia.

ASSESSMENTS

The main parameter for efficacy was the change in total score on the 17-item HDRS (Hamilton, 1960) between baseline and end-point. Secondary efficacy parameters were the Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) and CGI (Guy, 1976) total scores. To access and improve interrater reliability session using patient videotape have been organized. Those patients whose total HDRS or MADRS score, respectively, decreased by 50% from baseline were considered as 'responders'.

Published in : International Clinical Psychopharmacology (1998), vol. 13, n°3, pp. 121–128
DOI:10.1097/00004850-199805000-00005
Status : Postprint (Author's version)

Adverse events were recorded by open questioning at baseline and at each visit during the study. Their severity was rated as mild, moderate or severe, and their onset, frequency, duration and evolution were recorded. All adverse events were coded according to the WHO-ART dictionary.

STATISTICAL ANALYSIS

Descriptive analysis of the population and comparability of groups were studies using means (and standard deviations) and ANOVAs for quantitative variables, frequency and percentages, chi-squared global tests or extended Fisher's exact tests for qualitative variables.

Efficacy analyses are (1) Intent-to-Treat (ITT) analyses (all randomized patients who received study drug): Last observation carried forwards (LOCF) for end-point analysis, observed case (OC) for analysis by visit, and (2) per protocol (PP) analyses (all randomized patients who completed at least a 14 days treatment period, without major protocol violations).

The HDRS total and factor scores and the MADRS total score were analysed parametrically at each time point when the scales were rated. Analyses of covariance were performed, with country and baseline value as covariates. On the HDRS and MADRS, patients whose total score decreased by 50% or more from baseline were considered as responders.

Safety analysis was performed using X2 or fisher's exact test for comparisons between groups.

All tests of hypotheses were two-sided. The results were considered to be statistically significant at the alpha risk level of 0.05.

Results

A total of 311 patients were pre-included in this study. Among them, 300 were randomized, and 289 included in the ITT analysis: 93 patients in the milnacipran 100 mg/day group, 96 in the milnacipran 200 mg/day group, and 100 in the fluoxetine 20 mg/day group. The PP analysis was performed on 237 patients: 79 patients in the milnacipran 100 mg/day group, 75 in the milnacipran 100mg/day group, 75 in the milnacipran 200 mg/day group, and 83 in the fluoxetine 200 mg/day group.

COMPARABILITY OF STUDY GROUPS AT BASELINE

There were no significant differences at baseline between the three treatment groups with respect to demographic data, psychiatric history other than depression, medical and surgical history, time elapsed since first episode, duration of the current episode, or HDRS, MADRS and CGI-1 (severity of illness) scores (Table 1).

However there were significantly ($P < 0.05$) more patients at baseline in the milnacipran 200 mg/day versus the other two treatment groups who had made at least one suicide attempt and who had experienced recurrent episodes of depression.

Published in : International Clinical Psychopharmacology (1998), vol. 13, n°3, pp. 121–128
DOI:10.1097/00004850-199805000-00005
Status : Postprint (Author's version)

Table 1. *Mean (± SD) baseline characteristics of patients treated with milnacipran 100 mg/day, milnacipran 200 mg/day or fluoxetine 20 mg/day*

Parameter	Milnacipran 100 mg/day (*n* = 93)	Milnacipran 200 mg/day (*n* = 96)	Fluoxetine 20 mg/day (*n* =100)	*P* value[a]
Women/men[b]	60/40	66/34	75/25	NS
Age (years)	45.6 (12.4)	45.2 (12.5)	45.8 (12.8)	NS
Time since first episode (years)	9.4 (9.1)	8.3 (8.1)	7.0 (7.9)	NS
Time elapsed since previous episode (years)	4.9 (5.0)	6.4 (6.8)	2.6 (1.9)	0.003
Duration of current episode (weeks)	7.1 (5.2)	8.7 (9.3)	9.5 (15.5)	NS
HDRS total score	27.9 (3.8)	27.7 (4.4)	27.4 (4)	NS
CGI-1				
severely ill	30%	33%	39%	NS
markedly ill	62%	59%	57%	NS
MADRS score	32.2 (5.6)	31.9 (5.6)	32.1 (5.9)	NS
Previous suicide attempts	41%	51%	32%	0.03
Previous episode				
no	18%	6%	20%	
yes	82%	94%	80%	0.02

n included in the ITT analysis; NS not significant; [a]overall comparison; [b]randomised patients.

Table 2. *Percentage (and number) of patients withdrawing and reasons for withdrawal from treatment with milnacipran 100 mg/day, milnacipran 200 mg/day or fluoxetine 20 mg/day*

Reason	Milnacipran 100 mg/day (*n* = 93)	Milnacipran 200 mg/day (*n* = 96)	Fluoxetine 20 mg/day (*n* =100)
Patient decision	21.5% (20)	26.0% (25)	19.0% (19)
Lack of response	17.2% (16)	21.9% (21)	24.0% (24)
Adverse reaction	2.2% (2)	5.2% (5)	6.0% (6)
Suicide attempts	4.3% (4)	1% (1)	5% (5)
Suicides	1.1% (1)	1% (1)	1% (1)
Other serious adverse event	4.3% (4)	5.2% (5)	6.0% (6)
Intercurrent illness	1.1% (1)	4.2% (4)	1.0% (1)
Lost to follow-up	6.5% (6)	3.1% (93)	4.0% (4)
Other reason	9.7% (9)	8.3% (8)	12.0% (12)
Total	44.1% (41)	49.0% (47)	50.0% (50)

STUDY COMPLETION AND DROP-OUTS

The 12-week double-blind period of the study was completed by 56% of patients in the milnacipran 100 mg/day group, 51% in the milnacipran 200 mg/day group and 50% in the fluoxetine group.

Table 2 summarises the reasons for treatment withdrawal in each group. There were no statistically significant differences between groups with respect to the rates and reasons for withdrawal. However, there was a tendency for more patients in the fluoxetine group (6%) to withdraw prematurely because of adverse events; the percentage of patients to withdraw for this reason was lowest in the milnacipran 100 mg/day group (2.2%).

Published in : International Clinical Psychopharmacology (1998), vol. 13, n°3, pp. 121–128
DOI:10.1097/00004850-199805000-00005
Status : Postprint (Author's version)

Table 3. *Efficacy of treatment with milnacipran 100 mg/day, milnacipran 200 mg/day or fluoxetine 200 mg/day (intent-to-treat population)*

	Milnacipran 100 mg/day	Milnacipran 200 mg/day	Fluoxetine 20 mg/day	*P* value[b]
HDRS				
Initial score D0	27.8 (3.7) (n = 92)	27.7 (4.4) (n = 96)	27.4 (4.0) (n = 100)	NS
Final score D84	8.3 (6.5) (n = 53)	7.4 (6.4) (n = 52)	9 (6.5) (n = 54)	NS
Δ: D28 – D0	–15.2 (n = 78)	–14.0 (n = 73)	–12.4 (n = 77)	0.06
Δ: end-point – D0	–14.8 (9.8) (n = 92)	–12.9 (11.4) (n = 96)	–12.1 (10.0) (n = 100)	NS
Responders[a]	62 (n = 92)	54.2 (n = 96)	51 (n = 100)	NS
MADRS				
Initial score D0	32.23 (5.6) (n = 92)	32 (5.6) (n = 96)	32.1 (5.9) (n = 100)	NS
Final score	9.1 (8.4) (n = 54)	8 (8.0) (n = 52)	10.1 (8.8) (n = 54)	NS
Δ: D28 – D0	–18.2 (n = 78)	–16.3 (n = 73)	–14.4 (n = 77)	0.04
Δ: end-point – D0	–17.4 (12.3) (n = 92)	–15.8 (13.2) (n = 96)	–4.6 (12.1) (n = 100)	NS
Responders[a]	64.1 (n = 92)	55.2 (n = 96)	49.0 (n = 100)	NS

All data mean ± SD unless specified otherwise. [a]Percentage of patients whose total score decreased by ≥ 50%; [b]Overall comparison.
NS, not significant; data missing for 1 patient.

COMEDICATION

The most frequent concomitant medication used during the study were sedative/hypnotics, mainly benzodiazepines, prescribed to 80% of the patients. Oxazepam, proposed in the protocol as the preferable benzodiazepine, represents two thirds of this class, far ahead of clorazepate and prazepam.

EFFICACY

HDRS. HDRS total score for each of the three treatment groups is shown in Figure 1. Mean HDRS total score (Table 3) decreased significantly between D0 and the end of treatment and between D0 and each visit in all groups ($P < 0.001$).

There was no significant difference between groups for the change in HDRS total score between D0 and end-point. However, in the intent-to-treat (ITT) analysis there was a trend in favour of milnacipran 100 mg/day with respect to the change between D0 and D28 ($P = 0.06$), and the difference in the per protocol (PP) analysis was statistically significant (milnacipran 100 mg/day : HDRS score = 28.1 at baseline, change D28 – D0 = -15.2; milnacipran 200 mg/day: baseline score = 28, change = -14.4; fluoxetine 200 mg/day : baseline score = 27.4, change = -12.1) between D0 and D28 ($P = 0.03$). On the HDRS, a response (≥ 50% decreased in total score from baseline) by end-point was recorded in 62% of patients treated with milnacipran 100 mg/day, 54% of those treated with milnacipran 200 mg/day and 51% of those treated with fluoxetine 20 mg/day (not significant). No significant difference was observed between

Published in : International Clinical Psychopharmacology (1998), vol. 13, n°3, pp. 121–128
DOI:10.1097/00004850-199805000-00005
Status : Postprint (Author's version)

treatment groups in the ITT analysis of HDRS factors (Guy, 1976); however, in the PP analysis there was a significant difference for the 'anxiety/somatisation' factor, observed between D0 and d28 showing a greater improvement with milnacipran 100 mg/day (-4.6) and 200 mg/day (-4.5) than with fluoxetine (-3.4), ($P = 0.02$ and $P = 0.03$ respectively).

MADRS. In each treatment group, significant decreases from baseline were observed in the MADRS total score between D0 and each visit ($P < 0.001$). A significant difference was observed for the change between D0 and D28 in MADRS total score in ITT ($P = 0.04$) and PP analysis ($P = 0.02$) showing a greater improvement with milnacipran 100 mg/day compared with fluoxetine 200 mg/day. However, at end-point, this difference did not reach the significance level.

The percentage of MADRS responders at end-point (decreased of total score above 50%) was 64% in the milnacipran 100 mg/day group, 55% in the milnacipran 200 mg/day group, and 49% in the fluoxetine group. The difference between milnacipran 100 mg/day and fluoxetine was statistically significant ($P = 0.04$).

In summary, the three compounds were not different at end-point, although milnacipran 100/day was more efficacious on the MADRS at D28 compared with fluoxetine 20 mg/day.

CGI. With respect to three CGI factors (severity of illness, global impression and therapeutic index), there was no significant difference between treatment groups at any of the measured time points (ITT and PP analyses); however, a significant ($P = 0.01$) difference between groups was observed at D28 for CGI-3 (therapeutic index), the percentage of very good results being greater in the milnacipran 100 mg/day group (45%) than in the milnacipran 200 mg/day (22%) and fluoxetine (14%) groups. Moreover, at D28 there was a significant ($P = 0.03$, PP analysis) difference for CGI-2 (global impression), the percentage of patients who were 'very much improved' being greater in the milnacipran 100 mg/day group (39%) than in the milnacipran 200 mg/day (28%) and fluoxetine (14%) groups.

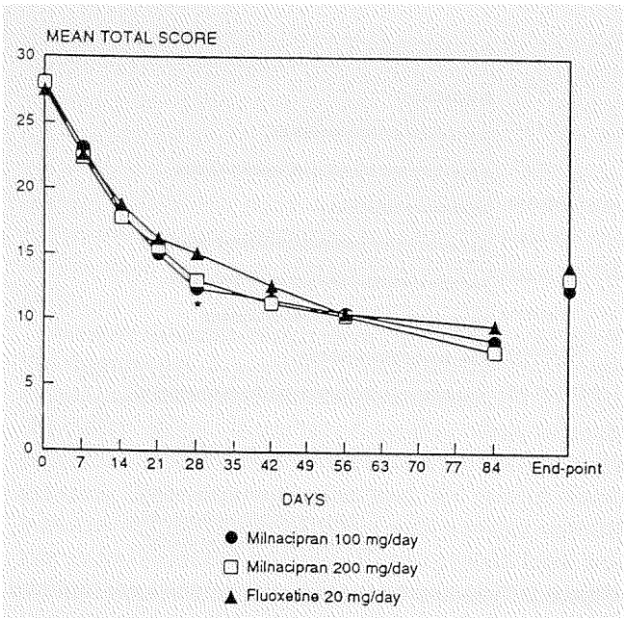

Figure1. Mean Hamilton Depression Rating scale total scores in th per protocol population (*significantly different between groups).

Published in : International Clinical Psychopharmacology (1998), vol. 13, n°3, pp. 121–128
DOI:10.1097/00004850-199805000-00005
Status : Postprint (Author's version)

SAFETY

The most frequent spontaneously reported adverse events (Figure 2) were as follows: milnacipran 100 mg/day – abdominal pain (13%), constipation (10%) and headache (9%); milnacipran 200/day - headache (8%), abdominal pain (7%), and nausea and vomiting (7%); fluoxetine - abdominal pain (11 %), nausea (11%), anxiety (10%) and insomnia (10%). In terms of cardiovascular safety, there was a statistically significant (P = 0.03) difference between the three treatment groups for tachycardia (heart rate 100 bpm) (fluoxetine, 0%; milnacipran 100 mg/day, 3%; milnacipran 200 mg/day, 6%). There were no significant changes in blood pressure. In terms of body weight, a significant ($P = 0.05$) difference between treatment groups was observed at D56, with a greater change with fluoxetine (-1.4 kg) than with either milnacipran 100 mg/day (no weight change) ($P = 0.02$ versus fluoxetine) or milnacipran 200 mg/day (-0.3 kg) ($P = 0.06$ versus fluoxetine).

Forty serious adverse events (SAEs) were reported during the study: 14 in the milnacipran 100 mg/day group, 10 in the milnacipran 200 mg/day group, 13 in the fluoxetine group, and three during the washout period. Most of the SAEs in the three treatment groups were related to the treated disease (suicide attempt, suicide, worsening of depression and anxiety). In the milnacipran 200mg/day group, there were fewer cases of attempted suicide ($n = 1$) and worsening of depression ($n = 2$) than in both the milnacipran 100 mg/day ($n = 4$ and $n = 5$, respectively) groups. There was ine suicide by hanging in each group : in the milnacipran 100 mg/day group, the patient was lost to follow-up, and she died 4 weeks after the theoretical end of the study treatment. In the milnacipran 200mg/day group, after an initial improvement (HDRS score decreased from 30 to 10 at week 2), the depression aggravated, requiring oxazepam, and the patient committed suicide after 4 weeks (HDRS score : 29). In the fluoxetine group, the suicide occurred after 6 weeks of treatment without noticeable HDRS modification (score at baseline = 29, at week 6 = 22), in spite of concomitant treatment with oxazepam + chloral.

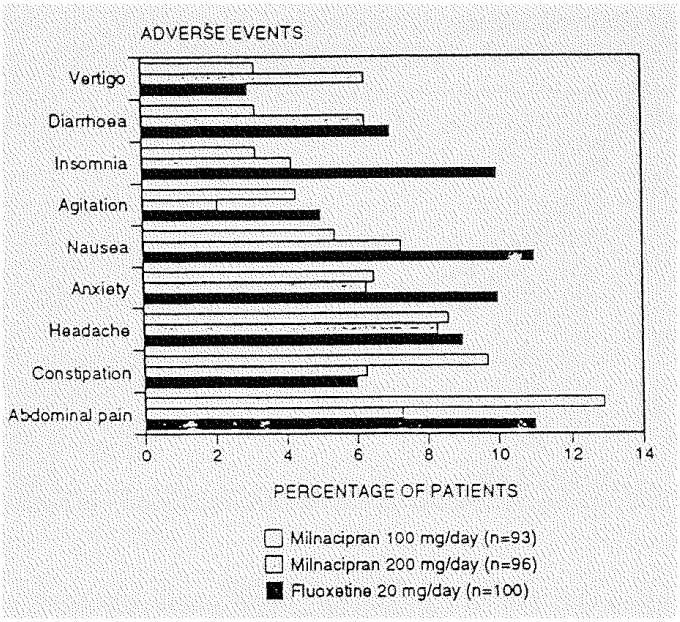

Figure 2. Type and frequency of spontaneously reported adverse events.

Published in : International Clinical Psychopharmacology (1998), vol. 13, n°3, pp. 121–128
DOI:10.1097/00004850-199805000-00005
Status : Postprint (Author's version)

Discussion

The present study was designed to evaluate the relative efficacy of two doses of milnacipran 100 mg/day and 200 mg/day and a standard reference treatment, fluoxetine 20 mg/day, in severely depressed inpatients.

Although not statistically significant, a difference in favour of milnacipran 100 mg was found on HDRS, the primary efficacy parameter.

In addition, there was a consistent trend in all the clinical parameters for an efficacy rank order favouring milnacipran 100 mg over 200 mg and fluoxetine 20 mg (milnacipran 100 mg/day > milnacipran 200 mg/day > fluoxetine 20 mg/day). Significant differences were found in favour of milnacipran 100 mg on HDRS (total score) and CGI-3 (therapeutic index) at D28, although they did not persist up to the end-point.

This study provides a direct comparison of milnacipran administered at daily doses of 100 mg and 200 mg. Although patients allocated to the highest dosage group met several criteria supporting a more severe pre-existing depression status (number of previous suicide attempts, percentage of patients with recurring depressive episodes), there was no trend in favour of the 200 mg dose being more active than 100 mg/day. Thus, the hypothesis that a higher daily dose of milnacipran may be more effective in severely depressed patients is not supported.

These date are nevertheless consistent with those observed in a fixed-dose parallel-group study comparing milnacipran 50, 100 and 200 mg/day with placebo in outpatients (unpublished data) and with those from several active-comparator studies using either 100 or 200 mg/day in which the lower dose yielded consistently better results than the higher dose.

While the patient groups assigned to treatment with either 100 or 200 mg/day doses of milnacipran were not strictly comparable in this study, the results suggest that increasing the daily dose, unlike the situation with other antidepressants (Puech, 1996), does not lead to a higher rate of efficacy.

In the present study, even if a trend exists in favour of milnacipran 100 mg/day, none of the milnacipran doses was significantly superior to fluoxetine with respect to the main efficacy parameter, HDRS total score. An important point to consider is the severity of the depression in this sample. The patients included were moderately to severely depressed, according to the inclusion criteria: hospitalization during at least one week, a minimum score of 22 on the HDRS-17, endogenous criteria according to the Newcastle Scale or the HDRS specific endogenous subscore, A CGI 1 (severity) rated moderately to extremely ill and the absence of DSM-III-R psychotic features (which presence is known to require the association of antidepressant and neuroleptic drugs). Other severity criteria may have been chosen, for example, DSM-III-R melancholia criteria (Clerc *et al.* 1994; Guelfi *et al.* 1995; Benkert *et al.* 1996). However, it should be stated that, as reflected by the HDRS and MADRS inclusion scores (34% of the patients having a HDRS score between 22 and 25, 41 % between 25 and 30, and 25% higher than 30), our criteria are relevant in terms of inclusion of moderate to severe depression.

Although questions may be raised with regard to the validity of drawing firm conclusions in the absence of a placebo reference, the results from this study should be considered along with

Published in : International Clinical Psychopharmacology (1998), vol. 13, n°3, pp. 121–128
DOI:10.1097/00004850-199805000-00005
Status : Postprint (Author's version)

those from other studies. First, both the difference in HDRS between baseline and end-point and the percentage of responders in the fluoxetine group in the present trial are quite similar to those reported in published placebo-controlled studies of fluoxetine administered at the same dosage in similar populations (Tollefson *et al.,* 1994; Hall, 1988). Similar findings have also been reported in active-comparator studies with fluoxetine (Beasley *et al.*, 1993; Song *et al.*, 1993). Therefore, it is unlikely that the difference between milnacipran and fluoxetine observed in this study is cause by an insufficient efficacy of fluoxetine in this population. Moreover, the 20mg/day fluoxetine dosage has been found as effective as higher (60 mg/day) dosages (Schweizer *et al.*, 1990) and has been considered as the optimal one (Altamura *et al.*, 1988). However, it can not be excluded that severely depressed patients could benefit from other treatment strategies or doses of fluoxetine, compared with milder forms. Nevertheless, a study of fluoxetine 40 mg/day in severely depressed patients has shown identical results as the present study (Clerc *et al.*, 1994).

Despite a relatively large sample size ($n = 289$) the observed differences were not statistically significant. Nevertheless, the magnitude of the difference at end-point, in particular between the milnacipran 100 mg/day and fluoxetine 20 mg/day groups (2.7 points on HDRS and 11% responders), may be of clinical value and it may reasonably be asked whether a slightly more powerful study would have led to statistically significant results, not only at one of the time points as shown here, but also at end-point.

Serious adverse events were generally related to the depression. Ten suicide attempts and three completed suicides occurred in this study, one in each treatment group: these three patients were severely depressed (baseline HDRS scores were 29-30), with previous depressive episodes, and, for two of them, previous suicide attempts. Even with a major suicidal risk as an exclusion criterion, how to project from suicide attempts remains a critical issue in all the studies including severely depressed patients.

In terms of safety profiles, there were no differences between milnacipran and fluoxetine, with the exception of tachycardia, which was significantly more frequent in milnacipran-treated patients, and anxiety, insomnia and weight loss, which were more frequent in patients who received fluoxetine 20 mg/day. Tachycardia, which appears to be dose-related, was probably associated with the noradrenergic component of milnacipran; this effect appeared to be moderate, reversible and well tolerated.

Conclusion

This 12-week double-blind, three-arm, randomised study in 289 inpatients with endogenous depression showed that milnacipran, administered at doses of 100 and 200 mg/day in a twice-daily regimen, is at least as effective and well tolerated as fluoxetine 200 mg/day in the treatment of major depressive episode. Although no statistically significant differences were recorded between treatments, there was a consistent tendency suggesting that milnacipran at a dosage of 100 mg/day may be a better candidate than either milnacipran 200 mg/day or fluoxetine 20 mg/day for the treatment of depression in terms of both efficacy and safety.

Published in : International Clinical Psychopharmacology (1998), vol. 13, n°3, pp. 121–128
DOI:10.1097/00004850-199805000-00005
Status : Postprint (Author's version)

References

Altamura AC, Montgomery SA, Wernicke JF (1988). The evidence for 20 mg a day of fluoxetine as the Optimal Dose in the Treatment of Depression. Br J Psychiatry 153 (suppl 3):109-112.

American Psychiatric Association (1987). Diagnostic and statistical manual of mental disorders. 3rd rev. ed. Washington DC; American Psychiatric Association.

Anseau M, von Fronckell R, Gérard MA, Mertens C, De Wilde J, Botte L, *et al.* (1991). Interest of a loading dose of milnacipran in endogenous depressive patients. Eur Neuropsychopharmacol 1:113-121.

Ansseau M, Papart P, Troisfontaines B, Bartholome F, Bataille M, Charles G, *et al.* (1994). Controlled comparison of milnacipran and fluoxetine in major depression. Psychopharmacology 114:131-137.

Beasley Jr CM, Holman SL, Potvin JH (1993). Fluoxetine compared with imipramine in the treatment of inpatient depression. Ann Clin Psychiatry 5:199-208.

Benkert O, Gründer G, Wetzel H, Hackett DA (1996). A randomized double-blind comparison of a rapidly escalating dose of venlafaxine and imipramine in inpatients with major depression and melancholia. P Psychiatr Res 30:441-451.

Clerc GE, Pagot JM, Bouchard JM, Oulès J, Guilbert M. Assicot M, *et al.* (1990). Therapeutic contribution of milnacipran and of clomipramine during a 3-month treatment: results of a comparative study. Psychiatric Psychobiologie 5:137-143.

Clerc GE, Ruimy P, Verdeau-Paillès J (1994). A double-blind comparison of venlafaxine and fluoxetine in patients hospitalized for major depression and melancholia. Int Clin Psychopharmacol 9:136-143.

Guelfi JD, White C, Hackett D, Guichoux JY, Magni G (1995). Effectiveness of venlafaxine in patients hospitalized for major depression and melancholia. J Clin Psychiatry 56:450-458.

Guy W (1976. Early clinical drug evaluation units. Assessment manual for pasychopharmacology. National Institute of Mental Health. Rockville, Maryland, USA.

Hall J (1988). Fluoxetine: efficacy against placebo and by dose – an overview. Br J Psychiatry 153 (suppl 3):59-63.

Hamilton M (1960). A rating scale for depression. J Neurol Neurosurg Psychiatry 23:56-62.

Kasper S, Plétan Y, Solles A, Tournoux A (1996). Comparative studies with milnacipran and tricyclic antidepressants in the treatment of patients with major depression : a summary of clinical trial results. International Clinical Psychopharmacology 11 (suppl 4):35-39.

Lecrubier Y, Plétan Y, Solles A, Tournoux A, Magne V (1996). Clinical efficacy of milnacipran. Placebo-controlled trials. Int CLin Psychopharmacol 11 (suppl 4):29-33.

Lopez-Ibor J, Guelfi JD, Plétan Y, Tounoux A, Prost JF (1996). Milnacipran and selective serotonin reuptake inhibitors in major depression. Int Clin Psychopharmacol 11(suppl 4):41-46.

Montgomery S, Asberg M (1979). A new depression scale designed to be sensitive to change. Br J Psychiatry 134:382-389.

Moret C, Charveron M, Finberg JPM, Couzinier JP, Briley M (1985). Biochemical profile of mildalcipran (F2207), a potential fourth generation antidepressant drug. Neuropharmacology 24:1211-1219.

Puech AJ (1996). A double action antidepressant: venlafaxine. Eur Neuropsychopharmacol 6 (suppl 4):45.

Published in : International Clinical Psychopharmacology (1998), vol. 13, n°3, pp. 121–128
DOI:10.1097/00004850-199805000-00005
Status : Postprint (Author's version)

Puozzo C, Leonard BE (1996). Pharmacokinetics of milnacipran in comparison with other antidepressants. Int Clin Psychopharmacol 11 (suppl 4):15-27.

Redmond AM, Kelly JP, Leonard BE (1995). The behavioural effects of milnacipran in the olfactory bulbectomised rad model of depression. Med Sci Res 23:533-534.

Roth M, Gurney C, Mountjoy CQ (1983). The Newcastle Rating Scale. Acta Psychiatr Scand 110 (suppl 1):42-54.

Schweizer E, Rickels K, Amsterdam J, Fox I, Puzzuoli G, Weise C (1990). What constitutes an adequate antidepressant trial for fluoxetine? J Clin Psychiatry 51:8-11.

Song F, Freemantle N, Sheldon TA, House A, Watson P, Long A, Mason J (1993). Selective serotonin reuptake inhibitors: meta-analysis of efficacy and acceptability. Br Med J 306:683-687.

Stenger A, Couzinier JP, Briley M (1987). Psychopharmacology of mildalcipran, a new potential antidepressant. Psychopharmacology 91:147-153.

Thase ME, Hersen M, Bellack AS (1983). Validation of Hamilton subscale for endogenomorphic depression. J Affect Disord 5:2567-278.

Tollefson GD, Holman SL (1994). How long to onset of antidepressant action: meta-analysis of patients treated with fluoxetine or placebo. Int Clin Psychopharmacol 9:245-250.