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Pooling Two Controlled Comparisons of Milnacipran (F2207) and Amitriptyline in Endogenous Inpatients

A new approach in dose ranging studies

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Milnacipran is a new potential antidepressant selected for its equipotent inhibition of noradrenaline and serotonin uptake and its lack of effect at any postsynaptic receptor. We recently compared milnacipran 100 and 50 mg/d and amitriptyline 150 mg/d in three parallel randomized groups of major depressive inpatients and found a statistically significant superiority of milnacipran 100 mg/d and amitriptyline over milnacipran 50 mg/d after 4 weeks of treatment. Later on we found similar improvement with milnacipran 200 mg and amitriptyline 150 mg but better tolerance with milnacipran.

In order to compare the therapeutic activity of the three doses of milnacipran (50 mg/d, 100 mg/d, and 200 mg/d) we used the responses to amitriptyline as a reference against which to compare the 3 doses of the new drug using analysis of variance on the adjusted data.

This approach reveals milnacipran 200 mg is more effective than milnacipran 50 and 100 mg and is the only dose which shows efficacy at least equivalent to that of amitriptyline 150 mg. The dose/efficacy relationship was linear.

Introduction

Milnacipran (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). In behavioural tests based on interaction with the noradrenergic system, such as antagonism of tetrabenazine-induced ptosis, potentiation of yohimbine-induced toxicity, and antagonism of apomorphine or oxotremorine-induced hypothermia, milnacipran is extremely active (Stenger *et al.*, 1987). Despite its structural resemblance to tranylcypromine, milnacipran has no effect on monoamine oxidase activity (Moret *et al.*, 1985).

This biochemical and pharmacological profile suggested that milnacipran might be a potent antidepressant devoid of anticholinergic side-effects. Indeed, it has been suggested that activity on both the noradrenergic and serotonergic systems may improve antidepressant activity (Van Praag, 1984).

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An open pilot study on 27 major depressed patients showed that milnacipran (100 mg daily) had a significant antidepressant effect within 7 days; in addition, the drug was well tolerated without antocholinergic side-effects (Serre *et al.*, 1986).

We recently compared milnacipran 100 and 50 mg/d and amitriptyline 150 mg/d in three parallel randomized 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*a*). However, the latency of the clinical improvement was somewhat longer with milnacipran that with amitriptyline, with a nonsignificant trend favouring amitriptyline after 2 weeks of treatment. We felt that this slower efficacy could be due to a too low dose of milnacipran used in this study performed in 144 severely depressed inpatients (Ansseau *et al.*, 1989*a*).

We therefore undertook a similar study to test if a higher dose of milnacipran (200 mg/d) could yield some benefit in comparison to the standard reference drug (amitriptyline 150 mg/d) in a sample of 87 endogenous severely depressed inpatients chosen with the same inclusion/exclusion criteria as in the previous study. We found similar improvement in both groups but better tolerance with milnacipran reflected in the better scores on the efficacy index of the CGI (Ansseau *et al.*, 1989*b*).

Therefore, the question arose of the statistical methodology which could be developed in order to compare the two studies and, principally, to compare the therapeutic activity of the three doses of milnacipran (50 mg/d, 100 mg/d, and 200 mg/d) as in a randomized dose ranging study.

Subjects and design

The subjects and the design of the study have been described in detail elsewhere (Ansseau *et al.*, 1989*a,b*). Briefly, the aim of this pooled study was to compare 3 doses of milnacipran studied, by the same investigators, in two separate controlled trials.

Data analysis

Instead of globally pooling the results obtained with amitriptyline and milnacipran in the 5 groups of patients (milnacipran 50 and 100 mg vs amitriptyline 150 mg, milnacipran 200 mg vs amitriptyline 150 mg), it seemed more appropriate to use the results under amitriptyline as a references against which to compare the 3 doses of milnacipran. Both amitriptyline groups were taken as baselines to adjust the results observed under milnacipran. At each assessment (day 0, 7, 14, 21, and 28), the respective mean scores of the amitriptyline groups were substracted from the individual scores obtained with milnacipran according to the trial group (i.e. the means observed with amitriptyline in the first trial were substracted from the individual data obtained with milnacipran 50 and 100 mg and the mean scores following amitriptyline in the second trial were substracted from the individual scores obtained with milnacipran 200 mg).

Thus, the data could be analysed in 3 groups instead of 5 because the variations with amitriptyline were mathematically reduced to zero. By pooling these 3 groups, a "pseudo dose-ranging" study was created and multivariate analysis of variance for repeated measurements could be performed. These analyses (SAS, 1985) were performed on the differences between the scores obtained at day 0 (baseline data) and those obtained at days 7, 14, 21 and 28 assuming that the response to treatment in the two study populations were independent of severity of illness and that the scores were normally distributed with the same co-variances among the two populations.

Three scores were studied: (1) the 24-item version of Hamilton Depression Scale; (2) the Montgomery and Asberg Depression Rating Scale (MADRS); (3) the efficacy index of the Clinical Global Impression (transformed score, range 0–4).

Results

Tables 1, 2 and 3 present, for each of the two trials, the means and standard deviations of the scores for the 5 groups before any adjustment. Due to the fact that the proportion of endogenously depressed patients is higher in the second trial (100% vs 88%), the initial scores of the rating scales are more elevated in the second experiment ($F(1,216)=9{\cdot}54$, $p=0{\cdot}01$ for the MADRS and $F(1,216)=16{\cdot}69$, $p=0{\cdot}001$ for the Hamilton depression scale). Nevertheless the basal values and the mean scores with amitriptyline are homogeneous within each.

TABLE 1. *Means and standard deviations for the global score of the Hamilton depression scale, by trial, by drug, and by day of assessment.*

	Trial I		
	Milnacipran		*Amitriptyline*
Days	50 mg (n=42)	100 mg (n=44)	150 mg (n=45)
0	33·6 (9·7)	32·1 (7·1)	33·4 (8·9)
7	26·5 (12·0)	23·7 (11·4)	24·8 (10·8)
14	22·1 (12·3)	19·5 (8·8)	17·7 (9·6)
21	18·1 (12·2)	15·3 (9·3)	13·8 (9·3)
28	15·3 (11·2)	12·0 (9·7)	11·6 (8·5)

	Trial II	
	Milnacipran	*Amitriptyline*
Days	200 mg (n=42)	150 mg (n=43)
0	37·3 (6·3)	37·6 (7·1)
7	29·8 (6·9)	30·3 (8·9)
14	22·0 (8.4)	21·5 (9·0)
21	17·7 (10·0)	17·5 (9·5)
28	14·2 (10·1)	16·7 (12·4)

TABLE 2. *Means and standard deviations for the global score of the MADR scale, by trial, by drug, and by day of assessment.*

	Trial I		
	Milnacipran		*Amitriptyline*
Days	50 mg (n = 42)	100 mg (n = 44)	150 mg (n = 45)
0	38·1 (7·3)	35·6 (7·8)	37·5 (7·8)
7	30·2 (9·7)	28·1 (11·1)	29·2 (10·6)
14	24·0 (10·9)	22·9 (8·8)	20·4 (10·1)
21	20·2 (11·2)	17·6 (9·8)	15·9 (9·5)
28	17·4 (11·8)	14·3 (10·7)	12·9 (8·2)

	Trial II	
	Milnacipran	*Amitriptyline*
Days	200 mg (n = 42)	150 mg (n = 43)
0	40·1 (6·3)	40·2 (6·9)
7	31·4 (6·3)	33·6 (9·1)
14	23·6 (8·7)	23·7 (9·5)
21	17·9 (10·2)	19·3 (10·6)
28	15·0 (10·7)	18·0 (13·3)

TABLE 3. *Means and standard deviations for efficacy index of the CGI scale, by trial, by drug, and by day of assessment.*

	Trial I		
	Milnacipran		*Amitriptyline*
Days	50 mg (n = 42)	100 mg (n = 44)	150 mg (n = 45)
7	1·71 (0·94)	1·62 (0·86)	1·47 (0·79)
14	1·89 (0·96)	1·81 (0·91)	1·80 (1·08)
21	1·95 (0·99)	2·27 (1·13)	1·91 (1·04)
28	2·30 (1·20)	2·49 (1·27)	2·12 (1·13)

	Trial II	
	Milnacipran	*Amitriptyline*
Days	200 mg (n = 42)	150 mg (n = 43)
7	1·50 (0·68)	1·18 (0·54)
14	1·81 (0·96)	1·61 (0·71)
21	2·22 (1·24)	1·82 (1·04)
28	2·53 (1·30)	1·89 (1·15)

As illustrated in Figs. 1 and 2, there was a clear relationship between the dose of milnacipran and the amelioration adjusted, as explained above, according to the results observed with amitriptyline. Statistically, the analyses of variance for repeated measurements performed on both Hamilton and MADR differences between pretreatment and days 7, 14, 21 and 28 scores showed a global difference between the 3 dosages; respectively, $F(2,109) = 2{\cdot}73$, $p = 0{\cdot}06$ and $F(2,109) = 3{\cdot}99$, $p = 0{\cdot}02$. Using the "*a posteriori*" Bonferroni test, these differences were most pronounced between 50 and 200 mg.

Furthermore, the correlations between the ameliorations computed between pretreatment and day 28 scores and the individual dose/kg yielded significant results in term of better improvement for higher doses: $r = 0{\cdot}27$, $df = 110$, $p = 0{\cdot}005$ and $r = 0{\cdot}21$, $df = 110$, $p = 0{\cdot}03$, respectively for the Hamilton and the MADR scales.

There was no statistical difference among the 3 dosages in the efficacy index of the CGI; nevertheless a significant correlation existed between the CGI index transformed data obtained at day 28 and the individual dose/kg: $r = 0{\cdot}20$, $ddl = 110$, $p = 0{\cdot}04$.

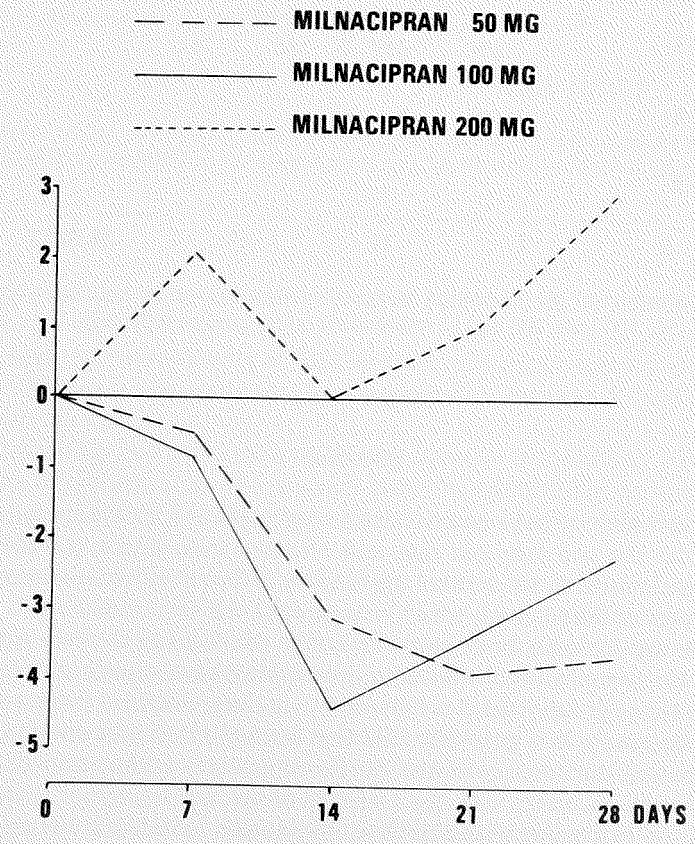

FIG. 1. Evolution of the MADRS total score by day and by dose of milnacipran (50, 100 and 200 mg) in reference to amitriptyline (150 mg).

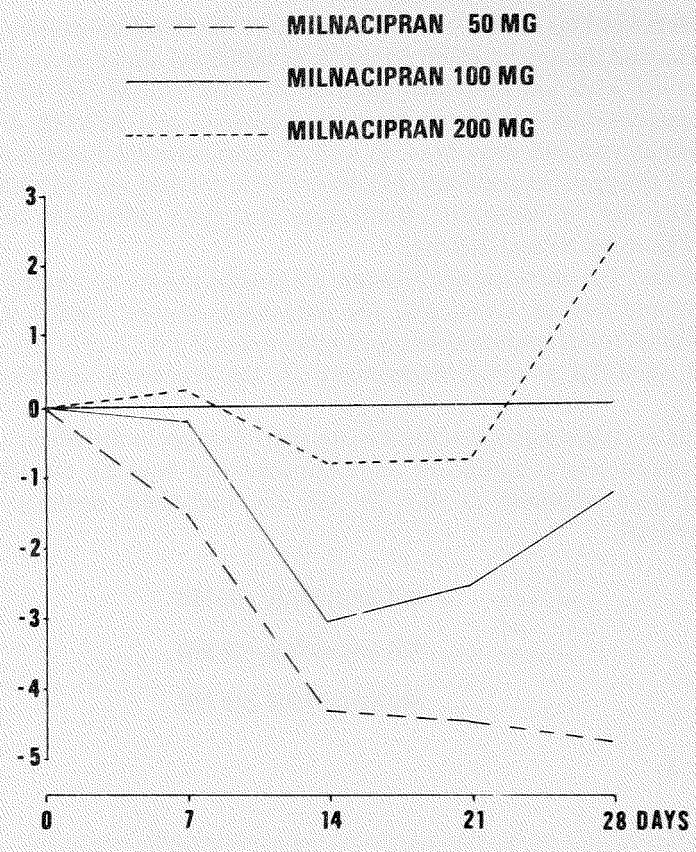

FIG. 2. Evolution of the Hamilton depression total score by day and by dose of milnacipran (50, 100 amd 200 mg) in reference to amitriptyline (150 mg).

Discussion

The analysis which we have undertaken is only applicable with populations which are of similar size and drop-out rate, and obtained from studies including similar patient populations. In the present application it clearly differentiates the efficacy of the 3 doses of milnacipran which were used in the two studies.

Despite the fact that both initial severities of illness in the two studies were dissimilar the comparison of scores for milnacipran-treated patients with those of the amitriptyline group yielded results similar to those obtained from a traditional dose-ranging study. It is generally held that during the clinical development of a new compound the severity of the depressed patients included in comparative controlled trials increases with the certitude of the antidepressant activity of the new molecule. In keeping with that view, the patients included in our second study were more severely depressed than those included in the first study. That is the reason why it is somewhat difficult to pool independent studies without having for

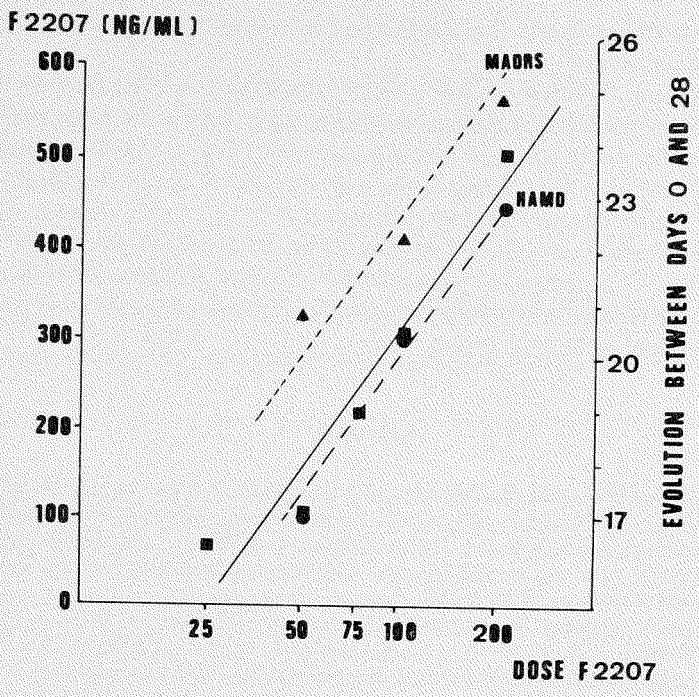

FIG. 3. Relationship between plasma level (ng/ml), doses of milnacipran (50, 100 and 200 mg) and efficacy (evolution between days 0 and 28, Hamilton depression and MADR scales).

each of them, a common reference measure by which it may be possible to compensate for such differences.

In our analysis, the sensitivity of the Hamilton rating scale appears greater than that of MADR scale, especially for the discrimination between 50 and 100 mg of milnacipran (see Fig. 2).

The relationship between dose and efficacy can also be related to pharmacological studies as illustrated in Fig. 3 which plots the relationship between dose of milnacipran and the plasma level in normal human volunteers (Solles, personal communication).

This figure also illustrates the relationship between the amelioration rated at day 28 on the MADR and Hamilton scales and the doses of milnacipran used in the 3 groups of depressed patients. Because the same range of doses was used in volunteers and in patients, these relationships can be exhibited on the same figure. The three curves are quite linear, monotonic, and parallel. The fact that no asymptotic relationship was observed in the dose/efficacy curves suggests that the individual dosages could be increased still further to improve the clinical activity of milnacipran.

Furthermore, the lack of any statistical difference between the three milnacipran groups on the efficacy index of the CGI while showing an excellent correlation between the individual dose/kg and this index (which possibly also

reflects tolerance), suggests that an increased dose of milnacipran up to 200 mg would be well tolerated.

In conclusion, this study shows a better antidepressant efficacy of milnacipran 200 mg compared with milnacipran 50 and 100 mg in major endogenous depressed inpatients without any tolerance problem as reflected by the CGI efficacy index. Based on the data for Figs. 1 and 2, the only dosage which shows efficacy at least equivalent to that of amitriptyline (150 mg) is 200 mg of milnacipran. The dose/efficacy relationship seems linear, as in more usual pharmacological dose/concentration studies. This method of pooling different controlled comparisons is able to reveal the dose/efficacy relationship in groups of inpatients constituted by samples of approximately 40 in each group.

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