Effect of high-dose milnacipran in patients with depression

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Abstract: To investigate the antidepressant effect of high-dose milnacipran, we retrospectively compared three groups of inpatients with major depression; those who were given milnacipran >100–150 mg/day (high-dose milnacipran group), those treated with milnacipran at maximum doses of 50–100 mg/day (standard-dose milnacipran group), and those treated with paroxetine at maximum doses of 40 mg/day (paroxetine group). The Hamilton Depression Rating Scale (HAM-D) scores of the three groups showed significant decrease at discharge compared to the scores at admission, indicating improvement of depressive symptoms for each group. However, the mean HAM-D score on admission was significantly lower for the standard-dose milnacipran group than the high-dose milnacipran and paroxetine groups. Additional intermediate assessment of the high-dose milnacipran group showed that the effect of milnacipran was dose-dependent with an additional improvement when patients were increase from 100 to 150 mg/day. These results suggest that patients suffering from moderate to severe depression with relative high HAM-D scores may benefit from treatment with high-dose milnacipran.

Keywords: milnacipran, dual-action antidepressant, high-dose, paroxetine, pharmacotherapy

Introduction

Milnacipran is a dual action antidepressant (serotonin and norepinephrine reuptake inhibitor) which is commonly used in Japan and some European countries. The antidepressant was introduced into Japan five years ago and it has been used as the first-line treatment for depression and depressive state alongside selective serotonin reuptake inhibitors (SSRIs). In Japan, the optimal dose of milnacipran is generally considered to be between 50 and 100 mg/day, and some European studies have reported that no marked differences were observed in response rates between the dosage of 100 mg/day and 200 mg/day (Serre et al 1987; Guelfi et al 1998). On the other hand, Puozzo et al (1985, 1996) showed that the blood levels of the drug increased in a dose-dependent manner from 25 to 200 mg/day and that milnacipran inhibited the reuptake of noradrenaline and serotonin in a dose-dependent manner at doses from 25 to 400 mg/day. In addition, Ansseau et al (1989) showed that the antidepressant effect of milnacipran was greater at 100 mg/day than 50 mg/day, suggesting a dose-dependent treatment effect.

The purpose of the present study was to further evaluate, in a clinical setting, the relationship between the antidepressant effect of milnacipran and its dose. In Japan, when a dose of milnacipran up to 100 mg/day fails to produce a sufficient antidepressant response, the patient is often switched to another antidepressant instead of receiving a higher dose of milnacipran. However, we have often encountered patients who have responded favourably to milnacipran at doses higher than 100 mg/day. Indeed, there have been several reports in Japan of the usefulness of treatment with milnacipran at doses exceeding 100 mg/day (Suzuki et al 2002; Morishita et al 2003; Kanemoto et al 2004). Von Frenckell et al (1990) showed that milnacipran given at a high dose of 200 mg/day was more effective than the

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standard-dose treatments (50 mg/day or 100 mg/day), and that 200 mg/day milnacipran was of comparable effectiveness to amitriptyline given at 150 mg/day.

The maximum doses of conventional tricyclic antidepressants range from 150 to 300 mg/day, while the upper limit of milnacipran dose has been set at 100 mg/day. This difference in maximum dosage may explain the apparent insufficient antidepressant effect of milnacipran which is sometimes found in some patients.

In the present study, we retrospectively selected inpatients diagnosed with a major depressive episode and classified them into two groups according to the dose of milnacipran received: standard treatment (100 mg/day or less) and high-dose treatment given at doses over 100 mg/day and up to 150 mg/day. We compared these patients with those treated with paroxetine, which is currently the most frequently prescribed antidepressant in Japan.

The present study was carried out in accordance with the principles of the Declaration of Helsinki.

Methods

The study was a retrospective case study of 84 consecutive depressive patients who were admitted to the psychiatry ward, Showa University Hospital during the period from April 1, 2004 to March 31, 2005. These 84 patients were diagnosed with major depressive episodes according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) by their psychiatrists. They were either antidepressant drug-naïve or off medication at least for one week on admission. Those who met the following criteria were included in the present study:

1. Received antidepressant treatment with either milnacipran or paroxetine as monotherapy.
2. Aged between 20 and 70 years.
3. Patients were classified into standard-dose treatment group if they had received the milnacipran at maximum doses from 50 to 100 mg/day; into the high-dose treatment group if they had been given milnacipran with a maximum dose of greater than 100 mg/day and up to 150 mg/day. Patients were excluded from the study if they had a maximum dose of milnacipran below 50 mg/day or received milnacipran treatment at the maximum dose for less than two weeks.
4. Patients given paroxetine were included if they had received the drug at a maximum dose of 40 mg/day for more than two weeks.
5. All patients were required to have available assessment data (HAM-D rating) on admission and at the time of discharge.

Patients were excluded if:

1. They met the diagnostic criteria of psychiatric diseases other than depression such as panic disorder, obsessive-compulsive disorder, and schizophrenic mood disorder according to DSM-IV.
2. They suffered serious heart, liver, or kidney diseases or suffered neurological diseases including cerebrovascular disorder and epilepsy.

A total of 49 subjects (16 males and 33 female) with a mean age of 57.1 ± 16.8 years were enrolled in the study (Table 1). Eighteen patients (6 males and 12 females; mean age 58.2 ± 15.1 years) were included in the high-dose milnacipran group. Their mean hospitalisation period was 111.6 ± 68.4 days. Sixteen patients (2 males and 14 females, mean age 57.5 ± 19.5 years) were included in the standard-dose milnacipran group. Their mean hospitalisation period was 65.8 ± 44.1 days. Fifteen patients (8 males and 7 females, mean age 55.5 ± 16.8 years) were included in the paroxetine group. Their mean hospitalisation period was 72.9 ± 56.8 days. The three groups were not statistically different for mean age or sex. The hospitalisation period for the high-dose milnacipran group was significantly longer than the other two groups ($p < 0.05$). Across all study subjects, concomitantly used drugs were as follows: anxiolytics in 22 patients (44.9%), and hypnotics in 33 patients (79.6%).

In order to retrospectively assess improvement of symptoms, the 21-item HAM-D scores obtained on admission and at the time of discharge were used. In the high-dose milnacipran group, the patients with HAM-D scores available during the period of treatment at doses from 50 to 100 mg/day were selected for the additional intermediate assessment, in addition to the assessments on admission (before receiving milnacipran) and at the time of discharge (milnacipran given at 150 mg/day for more than two weeks). HAM-D scores on admission, at the time of completion of the low-dose treatment, and during the high-dose treatment were available for 12 patients.

Stat View version 5.0 was used for the statistical analysis. Changes in HAM-D scores were analysed using two tailed t-test. All error values are given as the standard deviation.

Results

In the high-dose milnacipran group, the mean HAM-D score on admission and at the time of discharge were 26.9 ± 8.1 and 10.4 ± 5.6, respectively (Table 1). For patients who received paroxetine (40 mg/day), the mean HAM-D score on admission and at the time of discharge were 25.9 ± 7.6 and 10.8 ± 7.8, respectively. For these two groups, symptoms improved significantly and to a similar degree, indicating no significant inter-group

Table 1 Principal characteristics of the three patient groups

	Standard-dose milnacipran	High-dose milnacipran	Paroxetine
n	16	18	15
Sex ratio (male/female)	2/14	6/12	8/7
Age (years) (mean ± SD)	57.5 ± 19.5	58.2 ± 15.1	55.5 ± 16.8
HAM-D admission (mean ± SD)	21.1 ± 4.6*	26.9 ± 8.1	25.9 ± 7.6
HAM-D discharge (mean ± SD)	10.7 ± 5.4	10.4 ± 5.6	10.8 ± 7.8
Length of hospitalisation (days) (mean ± SD)	65.8 ± 44.1	111.6 ± 68.4*	72.9 ± 56.8

*<0.05 compared to the other two groups.

difference (Figure 1). In the standard-dose milnacipran group, the mean HAM-D score at the time of discharge also significantly improved to 10.7 ± 5.4 compared to admission. However, the mean HAM-D score on admission was significantly lower ($p < 0.5$) for the standard-dose milnacipran group (21.1 ± 4.6) than the high-dose milnacipran or paroxetine groups (Figure 1).

In 12 patients who started milnacipran at the standard-dose and subsequently increased to 150 mg/day, a dose-dependent two-step improvement of symptoms was observed (Figure 2).

Adverse effects occurred in one patient in the high-dose milnacipran group (nausea), and three patients in the paroxetine group (two cases of nausea and one case of tremor).

Discussion

HAM-D scores improved significantly during hospitalisation in both the standard-dose and the high-dose milnacipran groups. The improvement of depressive symptoms was comparable between the high-dose milnacipran group and the paroxetine 40 mg/day group. Retrospective assessment revealed that patients with higher HAM-D scores on admission were more likely to be given milnacipran at a dose of 150 mg/day. These findings suggest that patients with mild depression and low HAM-D scores on admission could be sufficiently treated with milnacipran at the standard-dose (50 mg/day to 100 mg/day), while patients suffering from moderate to severe symptoms demonstrated by higher HAM-D scores might need an increase in dosage of milnacipran up to 150 mg/day to improve their symptoms. This suggests that if a patient responds poorly to the standard-dose milnacipran treatment, it may be helpful to increase the dose up to 150 mg/day while assessing patient responses.

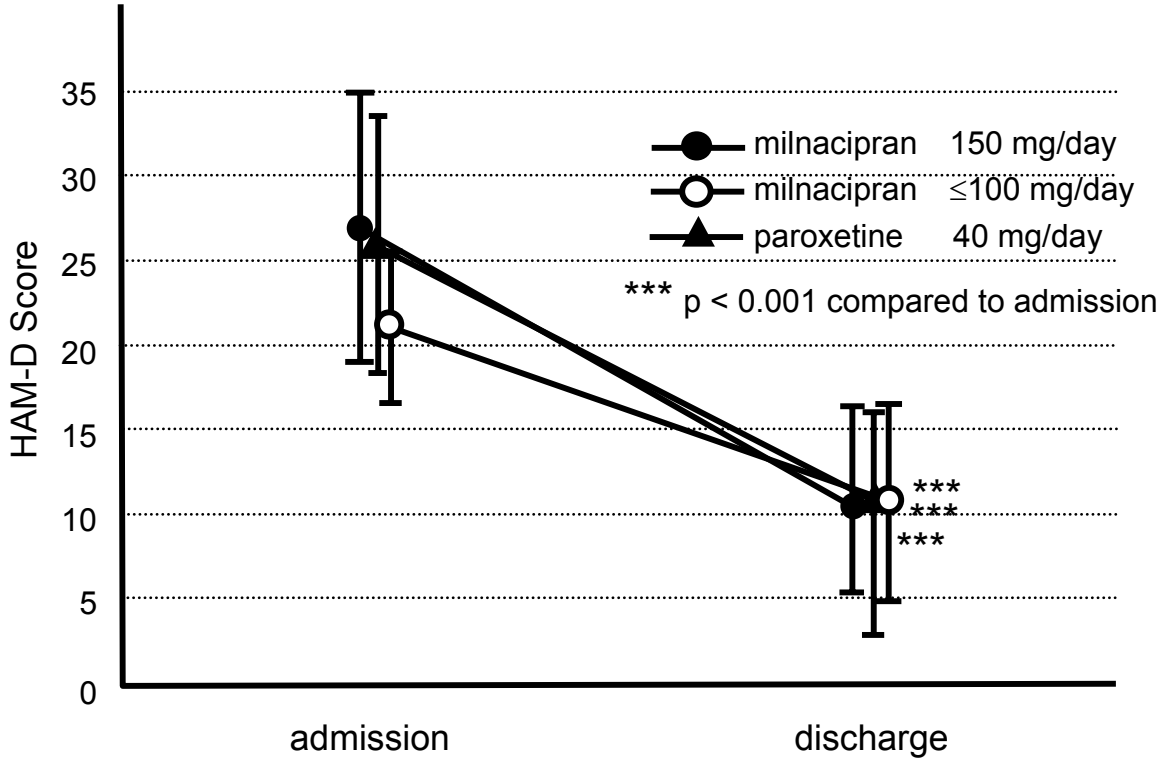

Figure 1 Changes in HAM-D scores after milnacipran treatment at doses of up to 100 mg/day and 150 mg/day and paroxetine at a dose of 40 mg/day *** indicate a significant difference ($p < 0.001$) from admission.

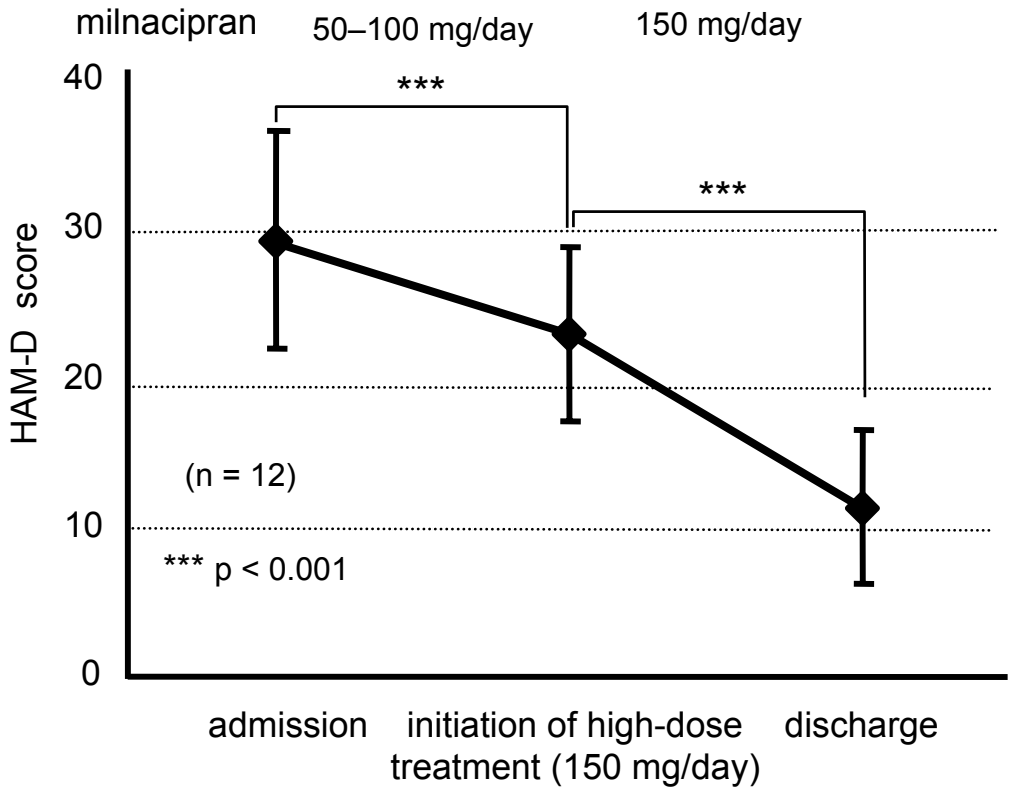

Figure 2 Changes in HAM-D scores in patients for whom milnacipran was increased to 150 mg/day. *** indicate a significant difference ($p < 0.001$) between the values indicated.

The present study has various limitations. In this retrospective study, there was no common scheme of dose escalation for milnacipran treatment. The timing of HAM-D assessment was not strictly controlled. In addition, only a small number of adverse effects were reported because none of the patients who had stopped treatment were included in the assessment. These "dropouts" should be included in the assessment in order to evaluate adverse effects directly caused by high doses of milnacipran. The limited number of patients together with possible effects of concomitant drugs in the present study are also weaknesses of this study. A prospective study designed to compare standard-doses of milnacipran and titration to higher doses in the Japanese context is clearly warranted.

Conclusion

The results of the present study suggest that patients suffering from moderate to severe depressive symptoms with relatively high HAM-D scores may benefit from two-step increment of milnacipran up to 150 mg/day.

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