

Plasma Levels of 3-Methoxy-4-Hydroxyphenylglycol and Relapse of Major Depressive Episode after Treatment with Milnacipran: One-Year Follow-Up Study

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Abstract

Objective: Plasma level of 3-methoxy-4-hydroxyphenylglycol (MHPG), a major metabolite of noradrenaline, is a useful biological marker for major depressive disorder (MDD). In the present study, we followed up plasma MHPG levels in remitted patients with MDD after milnacipran treatment.

Subjects and methods: Seventy-eight patients were diagnosed with MDD on the basis of the DSM-IV-TR criteria. The severity of depression was evaluated using the 17-item Hamilton Rating Scale for Depression (HAM-D17). Of the 78 patients, 29 had HAM-D17 scores of 7 points or lower after 8 weeks of treatment with milnacipran. These 29 patients were enrolled in the present study and followed up for one year. Their plasma MHPG levels were analyzed by high-performance liquid chromatography.

Results: Of the 29 MDD subjects, 17 relapsed within the one-year follow-up period. At the beginning of the follow-up period, plasma MHPG levels were significantly lower in the relapsed subjects than in the non-relapsed subjects.

Conclusion: Plasma MHPG level plays an important role in maintaining remission in MDD patients after treatment with milnacipran.

Keywords: 3-methoxy-4-hydroxyphenylglycol; Major depressive disorder; Milnacipran; Follow-up

Introduction

We previously reported that milnacipran, a serotonin noradrenaline reuptake inhibitor (SNRI), increased plasma levels of 3-methoxy-4-hydroxyphenylglycol (MHPG), a major metabolite of noradrenaline, in patients with major depressive disorder [1]. Milnacipran potentially inhibits both serotonin and noradrenaline transporters. Noradrenaline plays an important role in the pathogenesis of MDD. Our previous studies demonstrated that responses to antidepressants predict plasma levels of catecholamine metabolites [1,2]. In short, milnacipran monotherapy for 8 weeks significantly increased plasma MHPG levels, which were related to clinical recovery [1]. Of the 78 patients in that study, 36 remitted. I followed up those 36 patients for at least one year. Low levels of MHPG in cerebrospinal fluid reportedly predicted an increased suicide risk [3]. Kurita et al. [4] reported that plasma MHPG levels in patients with bipolar I disorder fluctuated according to their mood status; plasma MHPG levels decreased during depressive episodes and increased during manic episodes. Kurita et al. insisted that monitoring plasma MHPG is useful for predicting mood swing in bipolar I patients. Thus, MHPG is a useful biological marker for mood disorder. The object of the present study is to compare plasma MHPG levels at week 8 between subjects who would go on to remain in remission and those who would go on to relapse within a year. We consider that plasma MHPG level may be involved in remission or relapse in MDD patients who had been treated with milnacipran. We hypothesize that plasma MHPG levels at remission predict the relapse of depressive episodes in MDD patients. To confirm this hypothesis, we followed plasma MHPG levels in remitted patients with MDD who had been treated with milnacipran.

Subjects and Methods

Seventy-eight patients were diagnosed with major depressive disorder on the basis of the Structured Clinical Interview for DSM-IV

and the DSM-IV-TR criteria. The severity of depression was evaluated using the 17-item Hamilton Rating Scale for Depression (HAM-D17). Of the 78 patients, 29 had HAM-D17 scores of 7 points or lower after 8 weeks of milnacipran therapy, and these 29 patients were enrolled in the present study for one year of follow-up (Figure 1). The dosages of milnacipran varied among the patients and, based on ethical considerations, were not fixed. The dosage and duration of milnacipran were also shown in Figure 1. Exclusion criteria were any history of neurological diseases or other physical diseases, and comorbidities with other disorders, bipolar disorder or Axis II, personality disorders, and mental retardation by using Structured Clinical Interview DSM-IV Axis II. None of the subjects was administered antidepressants or benzodiazepines for at least one week before the study began. Blood sampling and clinical evaluation were performed at week 8. All subjects completed the study. All subjects were given information about the procedures. All subjects gave written informed consent via forms approved by the local Ethics Committee of the University of Occupational and Environmental Health. Plasma MHPG levels were analyzed by HPLC-ECD according to the method of Minegishi and Ishizaki [5]. In brief, the plasma was separated by centrifugation at 600 g at 4°C. Extraction was performed under a vacuum using Bond

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Elut columns (Varian, Palo Alto, CA, USA) prepacked with 100 mg of C18-bonded silica (40 μm) in a 1 mL capacity disposable syringe. The columns were prepared by washing with 1 mL methanol followed by 1 mL of water and then were inserted into a vacuum chamber connected to an aspirator. After the addition of 50 μl of a solution of vanillyl alcohol (internal standard equivalent to 5 ng/mL) to 1 mL of plasma, each sample was passed through a column, followed by 0.75 mL of water to rinse off both the sample residue and easily eluted hydrophilic compounds. The adsorbed materials were eluted with 200 μl of methanol to a 0.1 M phosphate buffer (pH 4.8) mixture (40:60, v/v). A 20-μL portion of this solution was injected into the HPLC. The detection limit was 0.5 ng/mL, and the calibration curve was linear up to 40 ng/mL. The intra- and inter-assay coefficients of variation were 6% and 8%, respectively. The recovery rate was more than 80%.

Statistical Analyses

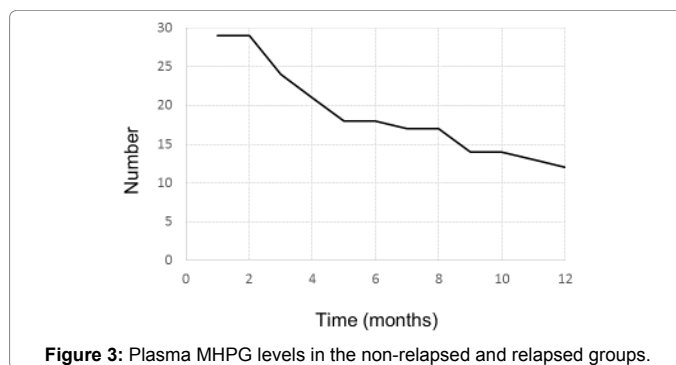
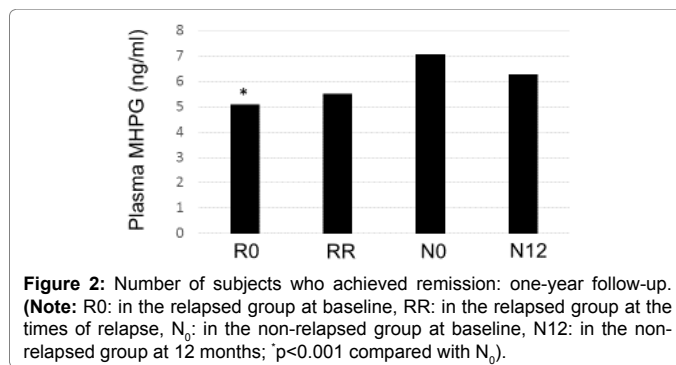
All statistical analyses were performed using STATA software. One-way ANOVA was performed to compare the groups. Bonferroni correction was used between each group and every other group. The level of statistical significance for all analyses was set at $p < 0.05$.

Results

Of the 29 MDD subjects, 17 relapsed within one year (Figure 2). Plasma MHPG levels at week 8 were significantly lower in the relapsed subjects than in the non-relapsed subjects. Among the relapsed subjects, plasma MHPG levels did not differ between week 8 and the point of relapse. Nor were there any differences in plasma MHPG levels of non-relapsed subjects between week 8 and one year after (Figure 3).

Discussion and Conclusion

The main finding of the present study was the significant difference at week 8 in plasma MHPG levels between the non-relapsed group and the relapsed group: the non-relapsed group had significantly higher levels. We previously reported that responders to milnacipran had significantly increased plasma MHPG levels. On the other hand, non-responders who were diagnosed with MDD did not show elevated levels. This suggests that milnacipran improves depressive symptoms at least by enhancing noradrenergic neurons. We also reported that, among MDD



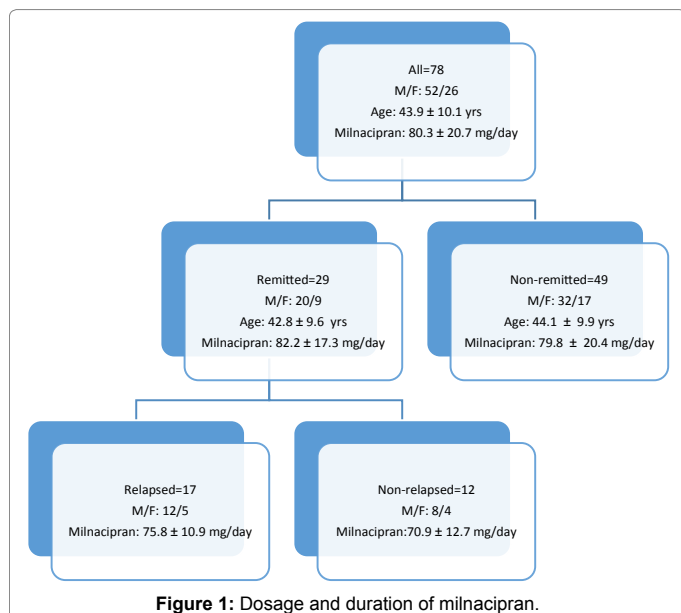
patients, responders to duloxetine, another SNRI, showed increased plasma MHPG at week 8, whereas selective non-responders did not. Taking these findings into account, we can see that noradrenaline plays an important role in alleviating depressive symptoms and also maintains remission. We speculated that its robust effect on noradrenergic systems leads to the prevention of relapse. Plasma MHPG was reflected in brain noradrenergic systems and peripheral sympathetic systems [6,7]. Kopin et al. [8] reported plasma MHPG in the central nervous system. Blier and Briley [9] reported that patients who had received a selective noradrenaline reuptake inhibitor had a significantly higher remission rate than patients who had received a selective serotonin reuptake inhibitor. A meta-analysis by Papakostas et al. [10] demonstrated that SNRI yielded slightly higher response rates than SSRI. These findings indicate that noradrenaline activity and sympathetic activity each play an important role in recovering from an alleviating depressive state and sustaining remission. Maintaining adequate plasma MHPG levels might be important for preventing patients with MDD from relapsing or at least patients who remitted during milnacipran treatment. The present study has several limitations. First, the sample size was small and the study was open. Second, the milnacipran dosages were not regulated. Third, the compliance of the subjects was uncertain. A restricted study with a larger sample is needed to confirm our preliminary results. In conclusion, adequate plasma MHPG levels are needed to maintain remission in MDD patients after treatment with milnacipran.

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