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Can Plasma Level of 3-methoxy-4-hydroxyphenylglycol Predict the Response for Selective Serotonin Reuptake Inhibitor and Serotonin Noradrenaline Reuptake Inhibitor in Major Depressive Disorder?

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Abstract

We investigated whether the plasma level of 3-methoxy-4-hydroxyphenylglycol (MHPG) could be used to predict the response to selective serotonin reuptake inhibitors (SSRIs) and serotonin noradrenaline reuptake inhibitors (SNRIs) in patients with major depressive disorder (MDD). Patients with MDD diagnosed by DSM-IV-TR were enrolled in the present study. Two hundred and forty participants were treated monotherapy with the SSRI paroxetine (n=81), selective serotonin and norepinephrine reuptake inhibitor antidepressant (SSNRI) duloxetine (n=49), the SNRI milnacipran (n=48), the SSRI fluvoxamine (n=63), or the SSRI escitalopram (n=27). The severity of depressive state was evaluated with the 17-item of Hamilton Rating Scale for Depression (HAMD17). The end-point point of the present study was week 8. Patients whose HAMD17 scores decreased ≥ 50% were defined as responders; others were non responders. Plasma MHPG levels were analyzed by high-performance liquid chromatography. A significant negative correlation was found between the change of plasma MHPG and the change of HAMD17 score in the responders to paroxetine or fluvoxamine. A trend for a positive correlation was found between the change of plasma MHPG and the HAMD17 score in the responders to milnacipran or duloxetine. These results suggest that MHPG might be a candidate for the prediction of treatment response in MDD patients.

Keywords: Major depressive disorder; SSRI: Selective Serotonin Reuptake Inhibitor; SNRI: Serotonin Noradrenaline Reuptake Inhibitor; MHPG: 3-Methoxy-4-Hydroxyphenylglycol; Response; HAMD17

Introduction

Depression is a serious mental illness requiring treatment. Major depressive disorder (MDD) is a complex disorder confounded by many bio psychosocial factors. Treatment with selective serotonin reuptake inhibitors (SSRIs) or serotonin noradrenaline reuptake inhibitors (SNRIs) is useful for MDD. The treatment of MDD requires collaborative efforts and holistic approaches by healthcare providers, public health interventions, and a reform in policies as well as the allocation of resources for the effective management of individuals with MDD, especially those with geriatric depression [1,2].

A major metabolite of noradrenaline, 3-methoxy-4-hydroxyphenylglycol (MHPG), passes the blood-brain barrier. It is thought that 30% to 60% of plasma MHPG originates in the brain. When administered to patients with MDD, some antidepressants increase plasma MHPG, whereas other antidepressants decrease or do not change the plasma MHPG level. We demonstrated that paroxetine, an SSRI, decreased plasma MHPG, and that the SNRI milnacipran increased plasma MHPG; we also reviewed the effects of several antidepressants on plasma MHPG levels [3-9]. We also found that plasma MHPG is useful for predicting relapse to a major depressive episode in MDD patients [8]. Another of our studies showed that switching from paroxetine to milnacipran did not alter plasma MHPG levels [9]. We conducted the present study to investigate whether MDD patients' responses to an SSRI and an SNRI can be predicted based on plasma MHPG.

Patients and Methods

Patients (n=240) with MDD diagnosed based on DSM-IV-TR were enrolled. All participants were undergoing monotherapy with the SSRI paroxetine (n=81), duloxetine, a selective serotonin and norepinephrine reuptake inhibitor antidepressant (SSNRI) (n=49), the SNRI milnacipran (n=48), the SSRI fluvoxamine (n=63), or the SSRI escitalopram (n=27). Only benzodiazepines were permitted during the study period. The patients (102 males, 138 females) were 42 ± 19 years old (mean ± SD). The severity of each patient's depressive state was evaluated with the 17-item Hamilton Rating Scale for Depression (HAMD17). The end-point point of the present study was week 8.

Patients whose HAMD17 scores had decreased by ≥50% at the study end-point were defined as responders; others were considered non-responders. Blood was drawn twice before and 8 weeks after the start of treatment. Plasma MHPG levels were measured using high-performance liquid chromatography (HPLC) with electrochemical detection according to the method reported by Minegishi and Ishizaki [10]. Briefly, the plasma was separated by centrifugation at 600 g at 4°C. Extraction was performed under a vacuum using Bond-Elut columns (Varian, Palo Alto, CA) pre packed with 100 mg of C18-bonded silica (40 μm) in a 1 mL capacity disposable syringe. The columns, which were inserted into a vacuum chamber connected to an aspirator, were prepared by washing with 1 mL methanol followed by 1 mL of water.

After the addition of 50 μL of a solution of vanillyl alcohol (internal standard equivalent to 5 ng/mL) to 1 mL of plasma, the samples were passed through the columns, followed by 0.75 mL of water to rinse off both residual sample and the easily eluted hydrophilic compounds. The

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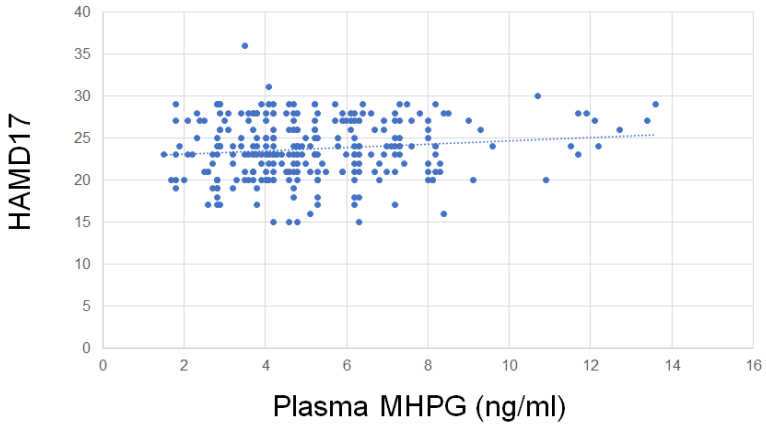

Figure 1: The HAMD17 and plasma MHPG at week 0.

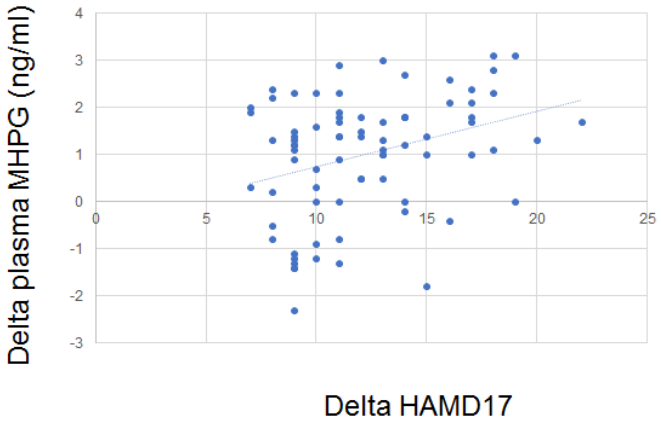

Figure 2: Delta plasma MHPG and the delta HAMD17 score in the 75 responders to SSRIs.

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 system. 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 >80%. The study protocol was approved by the Ethics Committee of the University of Occupational and Environmental Health. Written informed consent was obtained from all participants.

Statistical Analysis

The correlations between clinical variables and plasma MHPG were determined using Pearson's correlation. We calculated the cut-off value of MHPG by performing a receiver operating characteristic curve analysis. A p-value <0.05 was accepted as significant. All analyses were carried out using SPSS version 19.0 (SPSS Inc, Chicago, IL, USA).

Results

The demographic data of the patients are summarized in Table 1. The response rates for paroxetine, duloxetine, milnacipran, fluvoxamine, and escitalopram at the study end-point were 46/81 patients (56%), 22/49 (45%), 22/48 (45%), 29/63 (46%), and 11/27 (40%). No significant difference was found in plasma MHPG at week 0 between the SSRI group and the SNRI group. No significant differences in response rate were observed among the antidepressants.

The values of each patient's the HAMD17 and plasma MHPG at week 0 are plotted in (Figure 1). No association was observed between plasma MHPG at week 0 and HAMD17 score at week 0 (r=0.1843, p=0.781). A significant negative correlation was found between the change of (i.e., delta) plasma MHPG and the delta HAMD17 score in the 75 responders to paroxetine or fluvoxamine, and escitalopram (r=0.2972, p=0.031) (Figure 2). A trend for a positive correlation was found between the change of plasma MHPG and the HAMD17 score in the 44 responders to milnacipran or duloxetine (r=0.2209, p=0.074) (Figure. 3). The cut-off value of plasma MHPG, sensitivity, and specificity of each antidepressant are shown in (Tables 1 and 2). In other words, patients whose plasma MHPG levels were over 7.3 ng/mL (in the paroxetine group), under 7.7 ng/mL (milnacipran), under 6.4 ng/mL (duloxetine), over 6.1 ng/mL (fluvoxamine), or over 7.0 ng/mL (escitalopram) responded better to the respective antidepressants.

Discussion

In this patient population, the SSRIs (paroxetine, fluvoxamine, and escitalopram) changed the patients' plasma MHPG levels. Plasma MHPG was decreased from week 0 to week 8 in the responders to the SSRIs, whereas the plasma MHPG levels did not change in the responders to the SNRIs (duloxetine and milnacipran). A significant negative correlation was found between the change of plasma MHPG and the change of HAMD17 score in the SSRI responders. A trend for a positive correlation was found between the change of plasma MHPG and the HAMD17 score in the SNRI responders. These results are essentially in agreement with our previous findings [3]: the responders

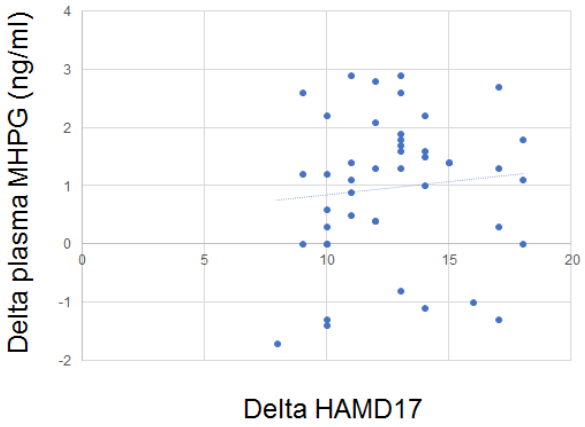

Figure 3: Delta plasma MHPG and the delta HAMD17 score in the 75 responders to SNRIs.

Variables	Paroxetine	Fluvoxamine	Escitalopram	Milnacipran	Duloxetine
	n=81	n=63	n=27	n=48	n=49
Males/females	39/42	28/35	13/14	25/23	20/29
Age, yrs (mean ± SD)	48 ± 15	42 ± 18	49 ± 16	45 ± 19	49 ± 17
Daily dose, mg (mean ± SD)	31 ± 10	74 ± 12	13 ± 4	81 ± 14	38 ± 19
Response rate (%)	46/81 (56%)	29/63 (46%)	11/27 (40%)	22/48 (45%)	22/49 (45%)
Baseline HAMD17	22 ± 14	24 ± 11	22 ± 14	25 ± 10	24 ± 13
Baseline MHPG (ng/ml)	7.2 ± 2.3	7.0 ± 2.9	6.8 ± 1.9	6.6 ± 2.6	6.9 ± 2.1

Table 1: Patient characteristics and response rate in each antidepressant group.

Anti-depressants	MHPG (ng/ml)	Sensitivity	Specificity
Fluvoxamine	6.1	68%	60%
Paroxetine	7.3	72%	59%
Milnacipran	7.7	79%	59%
Escitalopram	7.0	72%	69%
Duloxetine	6.4	82%	63%

Table 2: MHPG cut-off each anti-depressant.

to paroxetine showed significantly decreased plasma MHPG at week 4, whereas responders to milnacipran had significantly increased plasma MHPG at week 4 [3].

Egami et al. [11] reported that saliva MHPG levels in MDD patients were higher than those of healthy controls. They suggested that the baseline saliva MHPG level might be a predictive factor for SSRI. We also investigated cut-off values for the response to treatment with SSRIs and SNRIs. Unfortunately, the sensitivity and specificity values were not high enough. In other words, the plasma MHPG value was not robust enough to predict responses to SSRIs and SNRIs.

The main molecule for an SSRI is a serotonin transporter, which leads to continuous process. In other words, an interaction between serotonin and noradrenaline might be related to the present findings, or other factors such as dopamine might be associated with the results [12,13]. Phillips et al. [14] recently reported that the volume of the hippocampus may be influenced by serotonin- and norepinephrine-related gene polymorphisms. Taking these findings into account, we suspect that monoamines might influence each other in a complex manner, and SSRIs and SNRIs may both affect other proteins beyond their main target molecules.

Conclusion and Limitations

Our study has some limitations. We examined a heterogeneous patient series, in an open and not fixed-dose design; we had non-randomized controls, and there was a lack of parameters reflecting serotonergic neuron activities. In addition, the patients' genetic information was not obtained. Further studies should be conducted to test the findings of this preliminary study. However, our results indicate that plasma MHPG is a potential candidate for the prediction of MDD patients' responses to antidepressants. In general, SSRIs resulted in better responses by the present study's MDD patients with higher plasma MHPG levels, whereas treatment with the SNRIs resulted in better responses among the MDD patients with lower plasma MHPG levels.

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