Serum Brain-Derived Neurotrophic Factor Level, Plasma 3-Methoxy-4-Hydroxyphenylglycol Level in Major Depressed Patients with Paroxetine Monotherapy

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Abstract

Objective: We investigated the relationships among clinical efficacy, brain-derived neurotrophic factor (BDNF), 3-methoxy-4-hydroxyphenylglycol (MHPG), and paroxetine concentration in patients with major depressive disorder (MDD) who treated with paroxetine monotherapy.

Subjects and methods: Forty-nine patients in major depressive disorder diagnosed by Diagnostic and Statistical Manual of Mental Disorders-IV Text Revision (DSM-IV-TR) were enrolled in the study. All patients were treated with paroxetine for 8 weeks at a dose of 40 mg/day. Twenty-eight patients were completed the study. Their depressive symptoms were evaluated with the 17-item Hamilton Rating Scale for Depression (HAMD17). Plasma levels of MHPG and paroxetine were measured by high-performance liquid chromatography, and serum BDNF was measured by Enzyme-Linked Immuno Sorbent Assay (ELISA).

Results: Any correlations were observed between each factor.

Conclusion: Paroxetine concentration was independently in its clinical outcome and alteration of biological parameters.

Keywords: Brain-derived neurotrophic factor; 3-methoxy-4-hydroxyphenylglycol; Major depressive disorder; Paroxetine

Introduction

We previously reported paroxetine, a selective serotonin reuptake inhibitor (SSRI), influence catecholamine metabolites and brain-derived neurotrophic factor (BDNF) in patients with major depressive disorder [1]. In short, patients with better response to paroxetine treatment showed high plasma level of 3-methoxy-4-hydroxyphenylglycol (MHPG), a major metabolite of noradrenaline, and paroxetine treatment for 8 weeks increased serum level of BDNF.

Lundmark et al. [2] reported that paroxetine influenced cerebrospinal fluid noradrenaline metabolite level in depressed patients. To the best of our knowledge, this is the first study to investigate about the relationship between plasma SSRI level and plasma MHPG level, or serum BDNF level in major depressive disorder (MDD) patients with paroxetine.

In the present study, we investigated among clinical response to paroxetine, plasma paroxetine level, plasma MHPG level, serum BDNF level in Japanese MDD patients with paroxetine.

Subjects and Methods

Forty-nine patients in major depressive disorder diagnosed by DSM-IV-TR were enrolled in the study. Participants were collected between from January, 2008 to December, 2012. All patients were treated with paroxetine for 8 weeks at a dose of 40 mg/day. Their minimum and mean scores in HAMD17 were 18 and 23, respectively, which suggested their depressive states were moderate. Twenty-eight patients were completed the study. Their depressive symptoms were evaluated with the 17-item Hamilton Rating Scale for Depression (HAMD17). Plasma levels of MHPG and paroxetine were measured by high-performance liquid chromatography, and serum BDNF was measured by ELISA we previously described [3-5]. The demographic dates in details were shown in Table 1. 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.

| Participants | 28 |
|--------------|----|
| Male/Female  | 12/16 |
| Age (Yr)     | 48 ± 12 |
| HAMD17 (baseline) | 23 ± 3 |
| HAMD17 (8 weeks) | 12 ± 4 |
| BDNF (baseline) (ng/ml) | 8.9 ± 2.6 |
| BDNF (8 weeks) (ng/ml) | 10.5 ± 2.3 |
| MHPG (baseline) (ng/ml) | 6.2 ± 1.9 |
| MHPG(8 weeks) (ng/ml) | 5.7 ± 1.7 |

Table 1: The demographic data in participants.

Statistical Analysis

Relations between the clinical response, serum biomarkers, and paroxerine levels were analyzed using Spearman correlation. In addition, findings were corrected for multiple comparisons via Bonferroni correction. Significance of results was set at p<0.05.

Result

Changes of the HAMD17 scores and plasma MHPG levels

No association was found between the HAMD17 scores and plasma MHPG levels (rho=-0.0774, p=0.8413) (Figure 1).
Changes of the HAMD17 scores and serum BDNF levels

No association was found between the HAMD17 scores and serum BDNF levels (rho=0.0056, p=0.9981) (Figure 2).

Changes of plasma MHPG levels and serum BDNF levels

No association was observed between plasma MHPG levels and serum BDNF levels (rho=-0.1992, p=0.3187) (Figure 3).

Changes of the HAMD17 scores and plasma paroxetine levels

No association was observed between the changes of the HAMD17 and plasma paroxetine levels at week 8 (rho=0.2014, p=0.3129) (Figure 4).

Plasma paroxetine levels and the changes of plasma MHPG or serum BDNF levels

No association were observed between the changes of plasma MHPG (rho=-0.2491, p=0.3218), or serum BDNF (rho=0.1983, p=0.2391) (Figures 5 and 6).

Discussion

We found no relationships among the changes of HAMD, plasma MHPG, serum BDNF and plasma paroxetine level. We previously reported that plasma MHPG reduced in paralleled with the improvement of depressive symptoms in MDD patients with paroxetine responders not in the non-responders [1]. We also demonstrated that serum BDNF increased in paralleled with the improvement of depressive symptoms in the responders, not in non-responders [6]. The discrepancy between the previous studies and the present study may due to the fact that former studies dichotomized patients into two groups (responders and non-responders). Whereas, we dealt all data with patients treated with paroxetine monotherapy regardless in its response and we investigated the continuous variables for each parameter. The result that no association between plasma
paroxetine levels and the HAMD17 scores suggests that clinical efficacy of paroxetine is independent of the paroxetine concentration.

On the other hand, Tomita et al. reported the responder and remitter rates of the patients according to their plasma paroxetine concentrations: 20 ng/mL, 40 ng/mL and 60 ng/mL, and found the 20-60 ng/mL plasma paroxetine group showed highest response [7]. Yasui-Furukori reported that plasma paroxetine concentrations are negatively associated with improvement and that response occurs at the upper threshold of 64.2 ng/mL of paroxetine [8]. It still remains controversial whether or not paroxetine the plasma concentration is related to its clinical response. Also, the distribution of plasma paroxetine concentration was very wide even though same dose was administrated (data not shown). In addition, no correlation between plasma paroxetine levels and the changes of plasma MHPG or serum BDNF also mean plasma paroxetine levels do not influence above two biological markers, which changes in responders to paroxetine in MDD patients. Taken together, efficacy of paroxetine might be associated with mainly pharmacodynamics mechanisms, but not pharmacokinetic mechanisms. The present study was open label and without placebo control group. Therefore, any results are tentative and preliminary. The potential benefits of paroxetine should be confirmed in double-blind, placebo-controlled trials.

In conclusion, clinical efficacy of paroxetine in MDD patients was related with neither the plasma paroxetine level, plasma MHPG level, nor serum BDNF levels.

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