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Short communication

Long-term perospirone treatment with a single dose at bedtime in schizophrenia: Relevant to intermittent dopamine D₂ receptor antagonism

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Abstract

Perospirone, a serotonin 5-HT_{2A} and dopamine D₂ receptor antagonist, is metabolized to ID-15036 by CYP3A4 and the elimination half-life ($T_{1/2}$) for the latter is longer than the former. The active metabolite ID-15036 is an 8-times weaker D₂ antagonist than perospirone, although it has a high affinity for 5-HT_{2A} receptor. In this study, we measured the plasma concentrations of perospirone and ID-15036 in the long-term stable schizophrenic patients with a single dose of perospirone at bedtime. The mean level of perospirone at 11-15 hrs after a last dosing was much lower (0.49 ng/ml) than that of ID-15036 (2.89 ng/ml). These results show that a long-term perospirone monotherapy with a single dose at bedtime is effective for the maintenance treatment of chronic schizophrenia and also suggest the possibility that intermittent D₂ receptor blockade may be sufficient for effective relapse prevention.

Key words:

Perospirone; ID-15036; plasma concentration; maintenance; intermittent D₂ blockade; schizophrenia

Introduction

Perospirone is a serotonin 5-HT_{2A} and dopamine D₂ receptor antagonist originated in Japan. It has been considered that perospirone is metabolized to ID-15036 mainly by CYP3A4 based on *in vitro* (Mizuno et al. 2003) and *in vivo* study (Masui et al. 2006a; 2006b). Perospirone itself possesses a potent D₂ receptor blocking action similar to risperidone (Takahashi et al. 1998). However, its active metabolite ID-15036 is an 8-times weaker D₂ antagonist than perospirone, although it has a high affinity for 5-HT_{2A} receptor. On the other hand, both risperidone and its active metabolite 9-OH-risperidone bind with almost same affinity to D₂ receptor. It is reported that the baseline serum prolactin levels in patients receiving clinically effective doses of perospirone are much lower than those receiving risperidone (Togo et al. 2003; Yasui-Furukori et al. 2004). One of reasons for this discrepancy appears to be the difference in the active metabolites. That is, ID-15036 shows a high 5-HT_{2A}/D₂ ratio even at higher doses, which pharmacological profile is similar to that for clozapine (Matsubara et al. 1993; Takahashi et al. 1998).

Indeed, perospirone would be advantageous for avoiding EPS compared to risperidone, but how about the effect of this agent on relapse prevention in the maintenance treatment of schizophrenia? There have been several reports indicating that the relapse rate in the intermittent targeted treatment is higher than in the continuous maintenance treatment (Carpenter et al. 1990; Gaebel 1994). However, the difference was only marginal and of questionable clinical significance since these controlled trials failed to address a host of prognostic factors including patients' subjective experiences and acceptance of medication, mode of withdrawal of antipsychotic drugs, global functioning and quality of life, side-effect profile, premorbid social adjustment and stressful life events (Chan and Ungvari 2002). The PET study reported by Kapur et al.(2000) suggested that continuous blockade of D₂ receptors by antipsychotics is not essential for therapeutic effects. A speculation consistent with a paradigm of intermittent dosing would predict that the initial association of drug and receptor at the cell membrane triggers a chain of intracellular events (Boshes and Manschreck 2002). Therefore, intermittent dosing has been attracted attention as an alternative strategy (Boshes and Manschreck 2002).

Perospirone is metabolized to ID-15036 by CYP 3A4 and the elimination half-life ($T_{1/2}$) for the latter is 1.5 times longer than the former (Masui et al.2006b). After oral administration of 8mg perospirone, peak plasma concentration of ID-15036 is three times higher than that of perospirone in healthy subjects (Masui et al. 2006b). Thus, in the schizophrenic patients treated with a single dose of perospirone, it is expected that D₂ receptors may be intermittently blocked.

In this study, in order to examine the hypothesis that natural intermittent D₂ receptor blockade by perospirone is sufficient for a long-term maintenance therapy, we investigated the plasma concentrations of perospirone and ID-15036 in the long-term stable schizophrenic patients with a single dose of perospirone at bedtime.

Methods

Subjects

The subjects of this study were 10 outpatients (7 females and 3 males) with schizophrenia

defined by the Diagnostic and Statistical Manual of Mental Disorders, the fourth edition, Text Revision (DSM-IV-TR, American Psychiatric Association, 2000). Diagnosis was made through Mini International Neuropsychiatric Interview by experienced psychiatrists. Psychiatric assessments using Clinical Global Impression (CGI) and Global Assessment of Functioning (GAF) were completed monthly. The mean $\pm$ SD (range) of age was 40.9 ± 13.4 (25-58) years old. The mean duration of illness was 12.8 (4-42) years. All patients taking a single dose of perospirone at bedtime for a long-term antipsychotic monotherapy, have been kept a stable state (GAF score is 60 and more) for at least 2 years. An unstable state was defined as psychotic deterioration demanding a change in treatment, i.e. reinstitution of another drug, and GAF < 60 that persisted for two monthly ratings. None had taken any drug or food that affects CYP 3A4 activity. After complete description of the study, written informed consent was obtained from all subjects. The study protocol was approved by the Ethics Committee of Hokkaido University Graduate School of Medicine.

Measurement of the concentrations of perospirone and ID-15036

Blood samples (5 ml) were taken at 11-15 hr after last dosing. Plasma concentrations of perospirone and ID-15036 were measured by the high-performance liquid chromatography (HPLC) method reported by Yasui-Furukori et al. (2003). The lowest limits of detection and quantification were 0.1 and 0.2 ng/mL for both perospirone and ID-15036. And the values of the intra-day relative standard deviations were less than 3.4% for perospirone, and 3.7% for ID-15036, in the concentration range of 0.3-30 ng/mL.

Results

The mean follow-up period of perospirone monotherapy for stable outpatients was 42.6 ($\pm$ SD 14.9) months. The mean plasma concentrations of perospirone and ID-15036 at 11-15 hrs after the last dosing of perospirone (mean $\pm$ SD: 17.6 ± 9.7 mg) are shown in Table. The mean level of perospirone was much lower (0.49 ng/ml) than that of ID-15036 (2.89 ng/ml). The concentrations of perospirone were under lowest limit of detection in three patients, while that of ID-15036 in only one patient.

Discussion

The present study showed that the concentration of perospirone at 11-15 hrs after the last dose at bedtime was very low in the stable chronic schizophrenic patients treated with long-term perospirone monotherapy. On the other hand, the plasma level of ID-15036, an active metabolite of perospirone, was about 6 times higher than that of the mother compound. These results suggest that intermittent D₂ receptor blockade may be sufficient for effective maintenance treatment of schizophrenia since ID-15036 is an 8-times weaker D₂ antagonist than perospirone.

The concentrations of perospirone and ID-15036 in chronic schizophrenic patients were almost same as in healthy subjects reported by Masui et al.(2006b) although those with repeated treatment in this study were a little bit higher than with a single treatment in healthy subjects.

Even if plasma level of perospirone is not detected, there is a possibility that brain level of the

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compound is enough detected since elimination of perospirone from brain may be delayed compared to blood. Indeed, consecutive positron emission tomography (PET) study using [^{11}C]raclopride suggested that mean striatal D_2 receptor occupancies of perospirone were 74.8% at 1.5 hrs, 60.1% at 8 hrs, and 31.9% at 25.5 hrs after the administration of 16mg perospirone in healthy subjects (Arakawa et al. 2007). Whereas the plasma concentration of perospirone and ID-15036 were 3.8 and 16.0 ng/ml at 1.5 hrs, 0.6 and 1.8 ng/ml at 8 hrs, and 0 and 0 ng/ml at 25.5 hrs, respectively. Therefore, it is possible that stable schizophrenic patients with more than 0.6 ng/ml of plasma perospirone levels may show more than 60% of D_2 receptor occupancies.

The subjects in this study were all stable ($\text{GAF} \geq 60$) schizophrenic patients treated with a single dose of perospirone monotherapy at bedtime for more than 2 years ($\text{Mean} \pm \text{SD} = 42.6 \pm 14.9$ months). These findings may support the hypothesis that the intermittent D_2 receptor blockade may be more suitable to maintenance therapy of schizophrenia than continuous D_2 antagonism since the former can show as same effect as the latter on relapse prevention in spite of fewer extrapyramidal symptoms and hyperprolactinemia. Our study has some limitations such as small sample size and lack of control drug group with which to compare exacerbation rates during maintenance treatment. Thus, further investigations are needed to compare prospectively the effect on relapse rate between perospirone and continuous D_2 antagonist for a long period in a larger sample.

In conclusion, this study showed that long-term perospirone monotherapy with a single dose at bedtime was effective for the maintenance treatment of chronic schizophrenia. The present findings suggest the possibility that intermittent D_2 receptor blockade may be suitable to effective relapse prevention.

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Table. Mean Plasma Concentrations of perospirone and ID-15036 in the stable patients with schizophrenia

Patient	Gender	Age (years)	Diagnosis DSM-IV-TR	Duration of illness (years)	GAF score	ER followed-up period (months)	Stabilized PER dose (mg)	Time after last dosing (hr)	Mean plasma Concentration (ng/mL)	
									perospirone	ID-15036
1	Female	48	295.60	4	68	31	24	11	0.4	3.1
2	Female	58	295.60	42	76	38	16	13	0	0
3	Female	26	295.60	8	64	50	24	15	0.2	1.9
4	Female	54	295.60	20	88	62	16	11	1.5	10.2
5	Male	42	295.60	27	66	38	24	15	0.6	3.3
6	Female	42	295.30	4	62	36	32	13	0.5	4.2
7	Female	25	295.60	6	84	24	4	15	0	0.3
8	Male	26	295.30	5	60	60	24	12	1.1	4.7
9	Male	30	295.60	6	64	62	8	15	0	0.4
10	Female	58	295.30	6	68	25	4	15	0.6	0.8
Mean		40.9		12.8	70	42.6	17.6	13.5	0.49	2.89
SD		13.4		12.83917616	9.521905	14.85634919	9.651712571	1.715938357	0.497661197	3.077679501