Long-term Efficacy and Tolerability of Perospirone for Young Help-seeking People at Clinical High Risk: a Preliminary Open Trial

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Objective: Interest in the "at-risk mental state" (ARMS) for psychosis has increased because early intervention is expected to delay or prevent the onset of schizophrenia. However, the optimum intervention strategy remains controversial, especially with regard to antipsychotics. Although administration of antipsychotic medications is often associated with adverse effects and raises ethical considerations, recent studies have shown that some novel antipsychotics are safer and more tolerable for young people than conventional antipsychotics. We investigated whether administration of perospirone, a combined serotonin (5-HT)/dopamine antagonist and 5-HT1A receptor agonist, could alleviate prodromal symptoms and be well tolerated by clinical high risk patients.
Methods: The participants were outpatients seeking help. The Structured Interview for Prodromal Symptoms was performed in patients identified as being at clinical high risk. The Scale of Prodromal Symptoms (SOPS) was also completed and changes of subjective experience were assessed with the Subjective Well-being under Neuroleptics, short version. The incidence of akathisia was recorded by using the Barnes Akathisia Scale. Subjects were monitored for 26 weeks after starting medication.
Results: SOPS scores improved significantly after 26 weeks of perospirone therapy, while BAS scores did not show deterioration. No serious adverse events occurred during the study.
Conclusion: This trial suggests that perospirone therapy provides a clinical benefit for clinical high risk subjects without causing serious adverse events. Although further placebo-controlled studies are needed for confirmation, perospirone might be one of optimum treatments for individuals at imminent risk of psychosis.

KEY WORDS: Perospirone; Prodrome; Psychotic disorders; Early intervention; Schizophrenia.

INTRODUCTION

Interest in the clinical high risk state or "at-risk mental state" (ARMS) for psychosis has been increasing because early intervention is expected to delay or prevent the onset of schizophrenia. Recently, treatment that alleviates prodromal symptoms as well as preventing the onset of schizophrenia has attracted attention. It was reported that 35% of individuals meeting criteria for a psychosis risk syndrome made the transition to psychosis during a 2.5 year period.[1] Even if they do not undergo the transition to psychosis, many patients seek help because they are suffering from symptoms of ARMS. Addington et al.[2] found that about 40% of clinical high risk subjects who did not progress to psychosis continued to suffer from attenuated positive symptoms for 2 years, with their social and role functioning being significantly worse relative to those of non-psychiatric control subjects. Although these reports suggest that long-term therapy should be provided to clinical high risk patients seeking help, the optimum intervention strategy remains controversial, especially with regard to use of antipsychotics.

Recent controlled studies using antipsychotics have demonstrated a decrease of the conversion rate,[3,4] but most researchers and clinicians still hesitate to prescribe drugs for ARMS due to ethical considerations such as the risk of false-positive identification of ARMS and the adverse reactions related to pharmacotherapy. In fact, antipsychotics are often associated with adverse effects that are undesirable for young people, such as pronounced weight gain and sexual dysfunction.[3,5] While this clinical dilemma has been emphasized, antipsychotics tend to be prescribed for ARMS in the real-world setting. Cadenhead et al.[6] reported that psychotropic medications were

prescribed for 60.1% of patients at clinical high risk over their lifetime. Moreover, among those who had taken psychotropic medications, 23.7% had received an antipsychotic agent. In Japan, research based on the vignette has shown the possibility that many of the clinical high risk sample who were diagnosed as schizophrenia might be received an antipsychotic.[7] Similar research conducted in Singapore showed that most psychiatrists who diagnosed patients as being at clinical high risk chose to treat them with atypical antipsychotics.[8] Accordingly, antipsychotics are being prescribed for ARMS, and we should think about the efficacy and safety of pharmacotherapy.

A few recent studies on the psychosis prodrome have shown that some novel antipsychotics are safer and more tolerable for young subjects.[9,10] Perospirone is a combined serotonin (5-HT2)/dopamine antagonist and 5-HT1A receptor partial agonist that was developed in Japan, and it has been shown to be as effective as other antipsychotic agents for symptoms of schizophrenia.[11,12] The 5-HT1A receptor partial agonist activity of perospirone[13] could have an antianxiety effect and reduce adverse reactions such as extrapyramidal symptoms and weight gain.[14] In addition, activation of 5-HT1A receptors ameliorates a deficiency of dopaminergic neurotransmission in the frontocortical region in schizophrenic patients, which could improve the negative symptoms and cognitive deficits of schizophrenia.[15] Such pharmacological properties of perospirone may make it both effective and safer for clinical high risk patients.

Accordingly, this study was performed to investigate whether administration of perospirone for the treatment of psychotic prodrome was effective and tolerable in a help-seeking clinical high risk sample.

METHODS

Participants

This study was performed at the Toho University Omori Medical Center in Tokyo. All participants were help-seeking outpatients. They were eligible for enrollment if they were aged 15-39 years and fitted the Criteria of Prodromal Syndromes.[16] Patients were excluded from the study if they had (1) a previous diagnosis of any psychotic disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition;[17] (2) symptoms fully accounted for by an Axis 1 disorder or sequelae of drug/alcohol use; (3) abuse of alcohol or drugs; or (4) antipsychotic medication use. Adult participants gave written informed consent and minors gave written informed assent with consent from their parents. Data were collected between May 2009 and December 2010. This study was approved by the Ethical Research Committee of Toho University Omori Medical Center.

Procedures

During the week before beginning study medication, participants underwent eligibility assessment and examinations. After starting the medication, participants were monitored for 26 weeks.

Dosing was done according to a flexible schedule. Participants continued to take any antidepressants, mood stabilizers, or benzodiazepines that had been prescribed before the study (without changing the dose). Individual and family psychosocial interventions with supportive and psychoeducational components were available for each participant.

Measures

Clinical variables

The Structured Interview for Prodromal Symptoms (SIPS)[16] was performed in patients who were identified as having ARMS. We used the Japanese version of SIPS, which we previously demonstrated to have excellent interrater reliability.[18] Psychiatric measures included the Scale of Prodromal Symptoms (SOPS) and the Global Assessment of Functioning (GAF). The SOPS covers 4 categories of symptoms, which are positive, negative, disorganized, and general symptoms. Akathisia was assessed by using the Barnes Akathisia Scale (BAS).[19] Transition to psychosis was defined by using the Presence of Psychotic Symptoms criteria.[16] The SOPS was assessed at baseline, as well as after 2, 4, 6, 8, 13 and 26 weeks of treatment. The other measures and laboratory tests were investigated at baseline and after 4, 8, 13, and 26 weeks.

Assessment of subjective experience

Changes of subjective experience were assessed by using the Subjective Well-being under Neuroleptics, short version (SWNS).[20] The SWNS is a 20-item and 6-point Likert-type self-rating scale. Naber *et al.*[20] reported a 5-factor solution of the scale, which interpreted as emotional regulation, self-control, mental functioning, social integration, and physical functioning. We used the Japanese version of SWNS, which has demonstrated good reliability and validity.[21]

Statistical Analysis

All analyses were done on an intent-to-treat basis. If patients withdrew from the study, data were handled by the last observation carried forward (LOCF) method. Treatment effects were assessed with the paired *t*-test. We used one way repeated-measures analysis of variance (ANOVA) to test differences among the changes of scores, and Bonferroni's correction was employed on a post hoc basis. A probability of less than 0.05 ($p < 0.05$) was considered statistically significant for ANOVA and the *post hoc* tests. Calculation of descriptive statistics, ANOVA, and Bonferroni's test were performed with SPSS Statistics software (ver. 17.0; SPSS Inc., Chicago, IL, USA).

RESULTS

Eleven treatment-seeking prodromal patients (63.6% female, with a mean±standard deviation [SD] age of 26.7± 6.5 years) were enrolled in this study (intent-to-treat sample). Their demographic and clinical characteristics are presented in Table 1. Eight (72.7%) of the 11 patients had attenuated positive symptoms, 2 (18.2%) patients had

Table 1. Demographic and clinical characteristics of subjects

Characteristic	Data
Total number	11
Age (year)	26.7±6.5
Gender (female)	7 (63.6)
First-degree family history	1 (9.1)
Dropout	3 (27.3)
Type	
COPS-A (brief intermittent psychotic syndrome)	2 (18.2)
COPS-B (attenuated positive symptom syndrome)	8 (72.7)
COPS-C (genetic risk and deterioration syndrome)	0 (0)
COPS-B+COPS-C	1 (9.1)

Values are presented as number only, mean±standard deviation, or n (%).
COPS, Criteria of Psychosis-risk Syndromes

Table 2. Summary of clinical features

Case no.	Age (year)	Gender	Main clinical presentation
1	21	M	Suspiciousness, transient auditory hallucinations and hypobulia
2	39	F	Anxiety, feeling that she had incurred enmity of others
3	15	F	Suspiciousness, complained of hostility of classmates, and peculiar somatic complaints
4	27	F	Transient auditory hallucinations, vague sense of her thoughts being laughed at by others
5	25	F	Brief intermittent auditory hallucinations, insomnia, and perplexity
6	28	M	Susurrus aurium, transient auditory hallucinations, felt that others were talking about him
7	27	F	Peculiar somatic complaints, vague sense of her thoughts being known by others, and compulsive checking
8	27	M	Transient auditory hallucinations, emotional turmoil, and difficulty in expressing his thinking
9	25	M	Fear of others' eyes, peculiar somatic complaints, transient auditory hallucinations, and illusions
10	36	F	Interpersonal oversensitivity, feeling of being watched, and anxiety
11	24	F	Transient auditory hallucinations, vague anxiety, and emotional turmoil

M, male; F, female.

Table 3. Mean changes of SOPS, SWNS, GAF, and BAS scores from baseline to 26 weeks (LOCF analysis)

	Mean (SD)		Percent change	*p* value
	Baseline	26 weeks		
SOPS				
Total score	41.7 (6.5)	22.3 (18.7)	−20.1	<0.05
Positive symptoms	15.0 (2.1)	6.2 (7.4)	−9.2	<0.05
Negative symptoms	13.2 (3.1)	8.9 (6.1)	−4.6	NS
Disorganized symptoms	3.6 (2.2)	2.2 (1.9)	−0.9	NS
General symptoms	9.9 (3.1)	5.0 (5.1)	−4.9	NS
SWNS				
Total score	54.5 (11.1)	67.2 (12.1)	11.2	NS
Physical functioning	11.6 (2.4)	12.9 (3.8)	1.1	NS
Social integration	10.0 (2.6)	12.5 (2.7)	2.3	NS
Mental functioning	10.9 (3.3)	13.8 (3.2)	2.4	NS
Self-control	11.4 (3.2)	14.5 (4.0)	2.8	NS
Emotional regulation	10.5 (2.7)	13.5 (1.9)	2.6	NS
GAF scale	54.5 (14.9)	68.0 (11.6)	11.8	NS
BAS total score	0.2 (0.6)	1.6 (2.9)	-	-

SOPS, Scale of Prodromal Symptoms; SWNS, Subjective Well-being under Neuroleptics, short version; GAF, Global Assessment of Functioning; BAS, Barnes Akathisia Scale; LOCF, last observation carried forward; SD, standard deviation; NS, not significant.
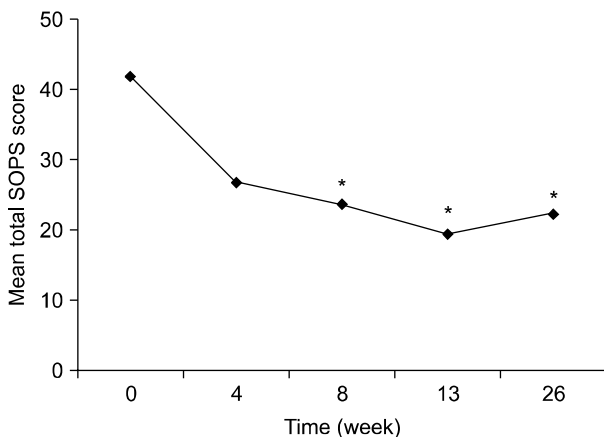
Fig. 1. Mean changes of total Scale of Prodromal Symptoms (SOPS) score from baseline in the patients. *$p < 0.05$.

brief intermittent positive symptoms, and 1 (9.1%) patient had attenuated positive symptoms combined with genetic risk and deterioration according to the SIPS. Table 2 provides a summary of the clinical features of the 11 subjects.

After 26 weeks of follow-up, 8 subjects (72.7%) remained in the trial. None of them converted to psychosis. LOCF analysis revealed significant improvement of the SOPS total score and positive symptoms score compared with baseline (Table 3). The change of the SOPS total score from baseline was statistically significant ($p < 0.05$) (Fig. 1). On the other hand, the SWNS total score (mean ±SD: 67.2±12.1; p=0.26) and the GAF scale (mean±SD: 68.0±11.6; p=0.57) did not show a significant change after 26 weeks (Table 3).

The mean±SD (chlorpromazine equivalent dose) daily dose of perospirone at baseline was 4.0±0.0 (50.0) mg, while the final mean±SD (chlorpromazine equivalent dose) daily was 10.2±6.0 (127.3) mg. The mean BAS total score returned to baseline by the final evaluation (Table 3). No serious adverse events including hyperglycemia or diabetes mellitus occurred during the study.

DISCUSSION

Perospirone was developed in Japan and has been marketed in this country for the treatment of schizophrenia since 2001. However, perospirone is not well-known outside Japan and could not be investigated in the international clinical practice guidelines established in 2005.[22] The present study showed the efficacy and tolerability of perospirone for patients at clinical high risk. Not all clinical high risk patients will convert to full-blown psychosis, so ethical problems are raised by prepsychotic in-

tervention, especially with regard to prescribing antipsychotics that have various adverse effects. However, help-seeking individuals who meet the clinical high risk criteria are already suffering from their psychotic symptoms, even if they do not have full-blown psychosis. In addition, attenuated positive symptoms vary in severity, which raises the question as to whether a common approach can be applied to the severer symptoms of patients at imminent risk for psychosis. Antipsychotic agents can be expected to improve the more severe attenuated positive symptoms. In the present study, perospirone improved the symptoms of clinical high risk patients without causing severe adverse effects. Our findings suggested that perospirone therapy may be of clinical benefit for individuals with ARMS and could be one of optimum treatments for those at imminent risk of psychosis.

Pharmacologically, perospirone is a combined serotonin (5-HT)/dopamine antagonist and 5-HT1A receptor agonist, so it may not only improve positive symptoms but also be effective against anxiety, negative symptoms, and cognitive deficits. Perospirone is less potent than other atypical antipsychotics like risperidone, and causes fewer adverse effects such as sedation or akathisia. Moreover, perospirone has a lower propensity to elicit metabolic side effects.[14] These pharmacological properties of perospirone might have been important for achieving such a favorable outcome in our mostly young and previously untreated clinical high risk patients.

The SWNS scores and the GAF scale tended to improve after 26 weeks, but did not change significantly from baseline. It was thought that these results might have been influenced by the higher functioning of individuals with ARMS at baseline. The mean dose of perospirone was below the dose range used to treat schizophrenia, and this could also have been associated with the clinical features of ARMS.

This study had some limitations. First, it was not blinded and was uncontrolled. Another limitation is the small number of subjects. Further research on perospirone is needed to provide confirmation that it can produce a clinical benefit in prodromal subjects.

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