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Original Article

Safety and Effectiveness of Perospirone in Comparison to Risperidone for Treatment of Delirium in Patients with Advanced Cancer: A Multicenter Prospective Observational Study in Real-World Psycho-Oncology Settings

Shinichiro Inoue[a], Isseki Maeda[b], Asao Ogawa[c], Kazuhiro Yoshiuchi[d], Seishi Terada[e], and Norihito Yamada[e]*

Department of Neuropsychiatry, [a]Okayama University Hospital, [e]Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama 700-8558, Japan,
[b]Department of Palliative Care, Senri-Chuo Hospital, Toyonaka, Osaka 560-0082, Japan,
[c]Department of Psycho-Oncology Service, National Cancer Center Hospital East, Kashiwa, Chiba 277-8577, Japan,
[d]Department of Stress Sciences and Psychosomatic Medicine, Graduate School of Medicine, The University of Tokyo, Bunkyo-ku, Tokyo 113-8655, Japan

The clinical benefit of perospirone for treatment of delirium in patients with advanced cancer is not sufficiently clear. The objective of this study was to compare the safety and effectiveness of perospirone to those of risperidone for the treatment of delirium in patients with advanced cancer. This is a secondary analysis of a multicenter prospective observational study in nine psycho-oncology consultation services in Japan. The study used the Delirium Rating Scale (DRS) Revised-98 to measure effectiveness and the CTCAE (Common Terminology Criteria for Adverse Events) version 4 to assess safety. Data from 16 patients who received perospirone and 53 patients who received risperidone were analyzed. The mean age was 70 years in the perospirone group and 73 years in the risperidone group. Both groups showed a significant decrease in the total score of DRS-R-98 after three days of treatment (perospirone: 11.7 (7.9-15.4) to 7.0 (3.3-10.7), difference −4.7, effect size = 0.72, $p = 0.003$; risperidone: 15.5 (13.6-17.4) to 12.2 (10.1-14.2), difference −3.3, effect size = 0.55, $p = 0.00$). The risperidone group showed significant improvements in sleep-wake cycle disturbance, orientation, attention, and visuospatial ability. In the perospirone group, there was a significant improvement of sleep-wake cycle disturbance. The median daily dose of perospirone was 4 mg/day. There were fewer episodes of somnolence as an adverse event in the perospirone group. Low-dose perospirone was thus found to be effective for the treatment of delirium in patients with advanced cancer and may be associated with fewer episodes of over-sedation as an adverse event.

Key words: delirium, cancer, perospirone, risperidone

Delirium is an acute brain dysfunction that can be caused by physical illness, drugs, or surgery. Delirium is characterized by a variety of symptoms, including attention disorder, sleep-wake cycle disturbance, emotional change, hallucination, and delusion. Delirium is characterized by short-lived symptoms that worsen at night.

Delirium creates a number of hindrances for patients, families, and medical professionals. For example, it is associated with falls, cognitive decline, and increased mortality [1, 2]. In addition, delirium

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*Corresponding author. Phone: +81-86-235-7242; Fax: +81-86-235-7246
E-mail: nyamada@okayama-u.ac.jp (N. Yamada)

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not only causes psychological distress for the family, but also increased medical costs, such as the expense of prolonged hospitalization [3,4].

In cancer patients, medications such as opioids and steroids are likely to cause delirium, and the frequency of delirium increases as the disease progresses. The prevalence of delirium is 42% at the time of admission to a palliative care unit, but reaches 88% before death [5].

In order to treat delirium, it is important to eliminate the cause. Non-pharmacological approaches, such as environmental adjustments, are also considered useful [6,7]. In addition, antipsychotic drugs are often used to reduce symptoms such as agitation, hallucination, and delusion [8,9].

Perospirone is an atypical antipsychotic developed in Japan that is mainly used for the treatment of schizophrenia. It is an antagonist of serotonin 5-HT2A and dopamine D2 receptors and has a pharmacological profile similar to that of risperidone [10,11]. Both perospirone and risperidone are classified as serotonin-dopamine antagonists (SDAs).

In addition to schizophrenia, delirium is also often treated with perospirone in Japan [12]. Haloperidol, quetiapine, risperidone, and perospirone are the four drugs that are approved for exceptional off-label use in Japan for the treatment of delirium. However, since perospirone was developed in Japan and has only recently come into use for the treatment of delirium, there are no high-quality studies on its efficacy and adverse events, either in Japan or overseas. In this study, we aimed to clarify the effectiveness and adverse events of perospirone in the treatment of delirium by comparing them with the effectiveness and adverse events of another SDA, risperidone, based on multicenter prospective data in patients with advanced cancer.

Materials and Methods

Settings. The Japan Pharmacological Audit Study of Safety and Effectiveness in the Real World was undertaken as part of a large-scale multicenter prospective study (Phase-R; study identifier: UMIN000018589). The study's procedures were described in detail elsewhere [13,14]. A total of 818 patients from 23 participating sites across the country (14 inpatient palliative care units and 9 psycho-oncology consultation services) were enrolled in the Phase-R delirium study between August 2015 and June 2016. In the palliative care units, palliative care physicians provided pharmacotherapy for delirium in patients with advanced cancer admitted to the palliative care ward. In the psycho-oncology settings, consultant psychiatrists provided drug therapy.

Participants. The study included consecutive individuals with delirium identified according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [15], who were scheduled to receive regular psychoactive agent administration (eight antipsychotics and trazodone) for delirium. Patients with withdrawal syndrome from alcohol or other psychoactive drugs, post-operative delirium, and delirious patients for whom palliative sedation was meant to decrease delirium symptoms were all excluded. Among the enrolled delirium patients, 69 patients were administered perospirone or risperidone in a psycho-oncology setting for the management of delirium symptoms, and were included in the present analysis.

Intervention. In the psycho-oncology settings at the participating sites, consultant psychiatrists generally performed the examinations of patients and the provision of pharmacological and non-pharmacological treatment. In order to reduce inter-institutional variability, consensus guidelines were developed for the diagnosis, severity assessment, and pharmacological and non-pharmacological treatment.

Measurements and procedures. Consultant psychiatrists conducted the assessments relevant to this study within the scope of routine clinical practice for seven days after the initiation of regular antipsychotic administration for delirium. Measurements were taken at three time points: day 0 (baseline assessment), day 3 (effectiveness assessment), and day 7 (safety assessment). If medications were changed during the course of the study, or if patients died or were discharged from the hospital, the last available data were used for safety and effectiveness assessments. For antipsychotics, only those administered on a regular basis were included in the evaluation.

At baseline, in addition to the diagnosis of delirium, patient characteristics, including age, gender, primary cancer site, central nervous system, dementia, clinician's prediction of survival (days, weeks, months), motor subtype of delirium, precipitating factors of delirium, and treatment settings were recorded. The diagnosis of delirium at baseline was made on the basis

of the DSM-5.

Outcome measures. On days 0 and 3, we assessed the severity of delirium based on the DRS-R-98 (Delirium Rating Scale-Revised-98 [16]). On days 3 and 7, we assessed adverse events according to the CTCAE (Common Terminology Criteria for Adverse On Events Version 4.0 [17]) and DIEPSS (Drug-Induced Extra-Pyramidal Symptoms Scale [18]). All assessments were performed by a consultant psychiatrist.

(1) DRS-R-98 (Delirium Rating Scale-Revised-98).

The DRS-R-98 is a scale used to assess the severity of delirium. The Japanese version of the DRS-R-98 is highly reliable and well validated [19]. This scale consists of 13 items: sleep-wake cycle disturbance, perceptual disturbance and hallucinations, delusions, lability of affect, language, thought process abnormalities, motor agitation, motor retardation, orientation, attention, short-term memory, long-term memory, and visuospatial ability. Each item was rated on a four-point scale of 0 (no impairment), 1 (mild), 2 (moderate), and 3 (severe). The higher the overall score, the higher the severity of delirium.

(2) Adverse events.

The CTCAE is an evaluation standard for adverse events. The presence of adverse events such as malignant syndrome, urinary retention, aspiration pneumonia, falls, somnolence, cardiovascular events, hyperglycemia, and sudden death, as well as their association with the drug were recorded. The causal relationship was rated on a 5-point scale of 1 (not related), 2 (unlikely), 3 (possible), 4 (probable), and 5 (definite). In accordance with NCI guidelines, adverse events with an assumed causal relationship of grade 3 or higher were recorded as severe adverse events [20].

The DIEPSS is a rating scale for extrapyramidal symptoms, which are side effects of antipsychotics, and consists of nine items: gait, bradykinesia, sialorrhea, rigidity, tremor, akathisia, dystonia, dyskinesia, and a global item. Each item was rated on a 5-point scale from 0 (nominal) to 4 (severe).

Statistical analysis. Descriptive statistics were used to show patient characteristics, precipitating factors of delirium, treatment effects, and adverse events. Line graphs were used to depict changes in DRS-R-98 total scores, and paired *t*-tests were used to compare pre–post results. In addition, the McNemar test was performed for each change in a symptom of delirium. SPSS version 25 (IL) was used for all analyses.

Ethical considerations. This study was carried out in conformity with the principles of the Helsinki Declaration. The protocol of this study was reviewed and approved by the ethical review committees of all participating institutions. Written informed consent was not required. Patients and their families learned about the study through posters and pamphlets, and they were given the option of declining to participate.

Results

Data collection. The data were collected between August 2015 and June 2016. The total number of patients enrolled at the end of the study was 818. Of these, 228 patients received pharmacotherapy for delirium in a psycho-oncology setting. Data from 16 patients who received perospirone and 53 patients who received risperidone were analyzed in detail.

Patient characteristics. The characteristics of the patients who received perospirone and risperidone are shown in Table 1. The mean age was 70 years in the perospirone-treated group and 73 years in the risperidone-treated group. There were more males than females in both groups. Table 1 shows the primary cancer sites in each patient. The number of patients with CNS lesions was 2 in the perospirone-treated group and 17 in the risperidone-treated group, and the number of patients with dementia was 1 in the perospirone-treated group and 7 in the risperidone-treated group. The most common prognosis for life expectancy was *months* in both groups. The most common motor subtype of delirium was hyperactive delirium in both groups. The median daily medication doses were 4 mg/day (interquartile range: 2.5-4 mg/day) of perospirone and 1.0 mg/day (interquartile range: 0.75-2.0 mg/day) mg of risperidone.

Precipitating factors of delirium. The precipitating factors of delirium are shown in Table 2. In the perospirone-treated group, the most common factors were infection, others, and drugs, in that order. In the risperidone group, the order was drugs, infection, and CNS lesion. In both groups, the number of causative factors was small, with the majority of patients having one or two. Only infection was significantly more common in the perospirone group ($p = 0.009$); there were no significant differences in the other factors.

Treatment effects of perospirone and risperidone.

Table 1 Patient characteristics

	Risperidone (n=53)	Perospirone (n=16)	Total (n=69)
Age, years	72.7±9.5	70.1±11.6	72.1±10.0
Gender			
Male	38 (71.7%)	13 (81.3%)	51 (73.9%)
Female	15 (28.3%)	3 (18.8%)	18 (26.1%)
Primary cancer site			
Lung	17 (32.1%)	2 (12.5%)	19 (27.5%)
Gastrointestinal	12 (22.6%)	3 (18.8%)	15 (21.7%)
Hepatobiliary	7 (13.2%)	3 (18.8%)	10 (14.5%)
Urological	4 (7.5%)	2 (12.5%)	6 (8.7%)
Breast	3 (5.7%)	1 (6.3%)	4 (5.8%)
Gynecological	1 (1.9%)	0 (0%)	1 (1.4%)
Others	9 (17.0%)	5 (31.3%)	14 (20.3%)
CNS lesion, yes	17 (32.1%)	2 (12.5%)	19 (27.5%)
Dementia, yes	7 (13.2%)	1 (6.3%)	8 (11.6%)
Clinician's prediction of survival			
Days	1 (1.9%)	0 (0%)	1 (1.4%)
Weeks	12 (22.6%)	1 (6.3%)	13 (18.8%)
Months	40 (75.5%)	15 (93.8%)	55 (79.7%)
Delirium motor subtype			
Hyperactive	27 (50.9%)	5 (31.3%)	32 (46.4%)
Hypoactive	8 (15.1%)	2 (12.5%)	10 (14.5%)
Mixed-type	8 (15.1%)	3 (18.8%)	11 (15.9%)
Unclassified	10 (18.9%)	6 (37.5%)	16 (23.2%)

CNS, central nervous system. Values are mean±SD or n (%).

Table 2 Precipitating factors of delirium

	Risperidone (n=53)	Perospirone (n=16)	Total (n=69)
Drugs	22 (41.5%)	7 (43.8%)	29 (42.0%)
Dehydration	7 (13.2%)	1 (6.3%)	8 (11.6%)
Infection	17 (32.1%)	11 (68.8%)	28 (40.6%)
CNS lesion	12 (22.6%)	3 (18.8%)	15 (21.7%)
Hypoxia	6 (11.3%)	2 (12.5%)	8 (11.6%)
Hepatic failure	5 (9.4%)	2 (12.5%)	7 (10.1%)
Renal failure	3 (5.7%)	0 (0%)	3 (4.3%)
Others	13 (24.5%)	5 (31.3%)	18 (26.1%)
Undetermined	3 (5.7%)	1 (6.3%)	4 (5.8%)
Number of underlying causes			
1	26 (49.1%)	6 (37.5%)	32 (46.4%)
2	15 (28.3%)	5 (31.3%)	20 (29.0%)
3 or more	9 (17.0%)	4 (25.0%)	13 (18.8%)

Values are n (%). CNS, central nervous system

The changes in the total DRS-R-98 score in the perospirone- and risperidone-treated groups are shown in Fig. 1. In the perospirone-treated group, the total score of DRS-R-98 decreased significantly from a baseline value of 11.7 after 3 days of treatment to 7.0 (difference −4.7, effect size=0.72, $p=0.003$). Also in the risperidone group, the total DRS-R-98 score decreased significantly from 15.5 to 12.2 after 3 days of treatment (difference −3.3, effect size=0.55, $p=0.002$).

The results for the DRS-R-98 subscales are shown in Table 3 as the change in prevalence in patients with a high severity of delirium (a score of 2 or higher for each

item). In both the perospirone- and risperidone-treated groups, the prevalence decreased for all items. In the perospirone-treated group, sleep-wake cycle disturbance ($p=0.03$) was significantly improved. Perceptual disturbances and hallucinations, thought-processing abnormalities, and orientation were not significantly different, but showed much improvement. In the risperidone-treated group, sleep-wake cycle disturbance ($p<0.001$), orientation ($p=0.05$), attention ($p=0.01$), and visuospatial ability ($p=0.04$) were significantly improved.

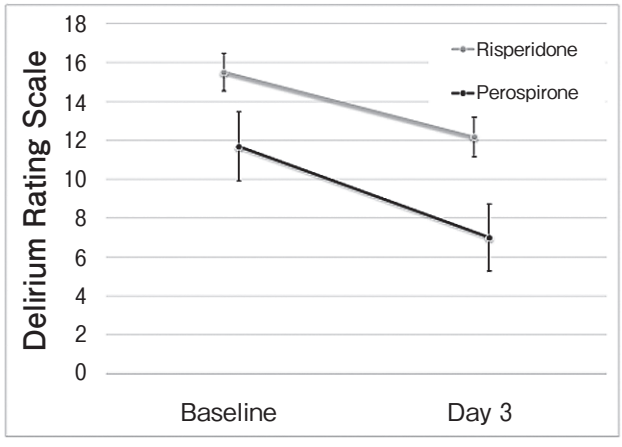

Fig. 1 Changes in the DRS-R-98 total score after risperidone (n = 53 patients) or perospirone (n = 16) treatment in the total population (n = 69). In the perospirone-treated group, the score changed from 11.7 (7.9-15.4) to 7.0 (3.3-10.7): difference −4.7, effect size = 0.72, $p=0.003$. In the risperidone-treated group it changed from 15.5 (13.6-17.4) to 12.2 (10.1-14.2): difference −3.3, effect size = 0.55, $p=0.002$.

Adverse events. The adverse events after administration of antipsychotics are shown in Table 4.

In the perospirone-treated group, 1 patient had somnolence and 1 patient had falls as possible drug-related adverse events. Only 2 patients had extrapyramidal symptoms, both of which were mild.

In the risperidone group, 3 patients died during the 7-day observation period. However, in the case of one of these patients, the prognosis for life expectancy was *days*, and in the other two cases the clinician judged the deaths to be due to the primary disease, and the likelihood of a causal relationship to the drug as *unlikely*. In the risperidone group, 8 patients had somnolence, and 2 patients had falls as possibly drug-related adverse events. Five patients had extrapyramidal symptoms, all of which were mild to moderate, except for one patient who had severe symptoms.

Discussion

In this study, we compared the effect of perospirone with the effect of another SDA, risperidone, on delirium and found that perospirone achieved a significant improvement in the total score of the DRS-R-98 compa-

Table 3 Changes in prevalence of each delirium symptom after antipsychotics administration

	Risperidone			Perospirone		
Delirium Symptoms	Baseline	Day 3	*P*-value*	Baseline	Day 3	*P*-value*
Sleep-wake cycle disturbance	69.8%	35.8%	<0.001	68.8%	31.3%	0.03
Perceptual disturbances and hallucinations	26.4%	22.6%	0.82	25.0%	0%	N/A
Delusions	17.0%	13.2%	0.73	18.8%	6.3%	0.50
Lability of affect	24.5%	13.2%	0.15	25.0%	18.8%	1.00
Language	30.2%	20.8%	0.36	18.8%	6.3%	0.50
Thought process abnormalities	26.4%	20.8%	0.61	12.5%	0%	N/A
Motor agitation	28.3%	15.1%	0.14	25.0%	12.5%	0.63
Motor retardation	20.8%	11.3%	0.13	18.8%	12.5%	1.00
Orientation	49.1%	32.1%	0.05	31.3%	6.3%	0.13
Attention	56.6%	34.0%	0.01	43.8%	18.8%	0.22
Short-term memory	41.5%	34.0%	0.42	31.3%	18.8%	0.50
Long-term memory	37.7%	30.2%	0.39	25.0%	12.5%	0.63
Visuospatial ability	43.4%	26.4%	0.04	12.5%	18.8%	1.00

Delirium symptoms were determined by using severity items of the Delirium Rating Scale (range 0-3 for each item). Proportion of patients with a score of 2 or greater (*i.e.*, moderate or severe symptom) is illustrated.
*p-values for McNemar test.

Table 4 Adverse events after administration of antipsychotics with "possible" or stronger causal relationship

	Risperidone (n = 53)	Perospirone (n = 16)
Death from all causes	3 (5.7%)	0 (0%)
Malignant syndrome	0 (0%)	0 (0%)
Urinary retention	0 (0%)	0 (0%)
Aspiration pneumonia	0 (0%)	0 (0%)
Falls	2 (3.8%)	1 (6.3%)
Somnolence	8 (15.1%)	1 (6.3%)
Cardiovascular	0 (0%)	0 (0%)
Hyperglycemia	0 (0%)	0 (0%)
Sudden death	0 (0%)	0 (0%)
Other SAEs	0 (0%)	0 (0%)
EPS (DIEPS overall)		
Mild	2 (3.8%)	2 (12.5%)
Moderate	2 (3.8%)	0 (0%)
Severe	1 (1.9%)	0 (0%)

NA, not applicable; SAE, serious adverse event; EPS, extrapyramidal symptoms

rable to that by risperidone. Risperidone is an atypical antipsychotic that has already gained a good reputation for the pharmacological treatment of delirium [21, 22]. The results of this study suggest that perospirone may be as effective as risperidone in the treatment of delirium.

It has been suggested that perospirone may improve sleep disturbances in delirium due to its ability to increase slow-wave sleep [10]. In the present study, the perospirone-treated patients exhibited a significant improvement of sleep-wake cycle disturbance ($p = 0.03$) as a symptom of delirium, suggesting that the pharmacological effects of perospirone may have been effective for improving sleep.

At baseline the total score of DRS-R-98 was 11.7 in the perospirone-treated group. Considering this result and the small number of precipitating factors of delirium, perospirone may be useful for relatively mild and recoverable delirium.

The Japanese package insert states that the clinical dose of perospirone is 4 to 48 mg/day. The median daily dose of perospirone in this study was 4 mg/day, suggesting that a low dose may be sufficiently effective.

In general, anticholinergic effects are known to exacerbate delirium [23, 24]. Perospirone has a low affinity for muscarinic M1 receptors, which are generally activated by anticholinergics, and thus perospirone may be advantageous.

Antipsychotics uniformly exhibit dopamine D2 receptor-blocking activity, and therefore they can exert anti-hallucinogenic and delusional effects via an increase in dopamine release. A typical side effect associated with dopamine D2 receptor blockade is extrapyramidal symptoms. Of the four major dopamine circuits, the nigrostriatal pathway is mainly associated with extrapyramidal functions. Every antipsychotic can inhibit dopamine function in this pathway, which causes drug-induced parkinsonism. Perospirone, however, has the advantage of being less likely to cause parkinsonism owing to its potent 5-HT2A receptor-blocking effect, which relieves dopamine hypofunction in the nigrostriatal pathway [10]. This is a major advantage in the treatment of delirium. In addition, among the extrapyramidal symptoms, parkinsonism is largely related not only to the strength of the dopamine D2 receptor-blocking effect but also to the length of binding time to dopamine receptors. Unlike that of risperidone, the antagonistic effect of perospirone on dopamine D2 receptors is limited to a short time [25]. In other words, when administering perospirone once a day, the dopamine D2 receptor blocking effect will be strong immediately after administration, and then will gradually weaken until the next dose. The results of this study suggest that patients administered perospirone are less likely to develop parkinsonism than those administered risperidone; if this is true, the lower incidence of parkinsonism may be related to such pharmacokinetics.

Since motor agitation is often observed as a symptom of delirium, a certain degree of sedation is required for the drugs to be administered. The sedative effects of antipsychotics are strongly related to their effects on H1 and α1-adrenergic receptors. Both risperidone and perospirone have a high affinity for H1 receptors and may

be useful in the treatment of delirium. However, it is necessary to avoid over-sedation in some cases, such as elderly patients or physically critical patients.

In regard to the affinity for α1-adrenergic receptors, the Ki value of risperidone is 2.3, while that of perospirone is 17, which is quite weak [26]. This difference in Ki values may have led to the present finding that perospirone caused less somnolence than risperidone. Therefore, perospirone may be more useful than risperidone in patients with delirium in whom over-sedation by pharmacotherapy is to be avoided. The profile of delirium was different between the perospirone- and risperidone-treated groups. For example, the perospirone-treated group had less hyperactive delirium and fewer CNS lesions or dementia than the risperidone-treated group. This feature may make perospirone the drug of choice in real-world practice.

Since this study is an observational study conducted in the real world, the history of each patient varied greatly. Therefore, factors other than pharmacotherapy may have played a role in our results. It is also possible that the content of non-pharmacological interventions [6, 8] or concomitant use of sleep medications (*e.g.*, benzodiazepines) [27, 28] may have affected the severity and course of delirium. Moreover, in order to reduce inter-institutional variability, consensus guidelines were developed and shared prior to the start of the study, but it cannot be guaranteed that these guidelines were fully followed. In addition, the 3-day treatment period may have been too short to determine the efficacy of pharmacotherapy, so caution is needed in determining the clinical significance of the study. In general, however, most studies evaluating drug efficacy for delirium in the palliative care field are conducted under limited time conditions, and at least one other study evaluated the efficacy of a drug for delirium using a treatment period of 3 days [29].

Perospirone is an atypical antipsychotic that is expected to be as effective as risperidone in reducing the severity of delirium in patients with advanced cancer. It may be particularly useful in patients with mild and highly recoverable delirium. In addition, not only is it sufficiently effective at low doses, but it may also have fewer side effects, such as parkinsonism and over-sedation. It is hoped that further clinical studies with larger populations will be conducted in the future.

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