Progress in Neuro-Psychopharmacology & Biological Psychiatry 35 (2011) 537–540

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Risperidone oral solution versus standard tablets for the acute treatment of patients with schizophrenia

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ARTICLE INFO

Article history:
Received 29 September 2010
Received in revised form 24 November 2010
Accepted 10 December 2010
Available online 17 December 2010

Keywords:
Effectiveness
Oral solution
Risperidone
Schizophrenia
Standard tablet

ABSTRACT

The time required to attain the maximum plasma level of risperidone (RIS) is shorter for RIS oral solution (OS) than for RIS standard tablets (ST), although both forms have equal bioavailability. The objective of this study was to clarify whether RIS-OS shows a faster onset of efficacy and lower adverse events than RIS-ST. The two forms of risperidone were compared with respect to effectiveness including a speed of response, efficacy and tolerability. An open-label, 24-week, multicentre, randomized, flexible-dose study comparing the RIS-OS (mean dose, 3.7 mg; N = 44) to the RIS-ST (mean dose, 3.7 mg; N = 37) in acutely ill patients with schizophrenia showed no differences. Outcome measures included psychopathology, tolerability (extrapyramidal symptoms and serum prolactin), and Drug Attitude Inventory. This study was conducted between October 2006 and October 2008. Both RIS-OS- and RIS-ST-treated patients showed statistically significant reductions from the baseline in the mean scores of the Positive and Negative Syndrome Scale (PANSS)-total and PANSS-excite component, with no statistically significant differences between the treatment groups. The accumulated treatment response ratio was similar between the two groups. There was no significant difference in the Drug-Induced Extrapyramidal Symptom Scale score or serum prolactin increase between the treatment groups, but RIS-OS appeared to induce less serum prolactin increase than RIS-ST in drug-naïve female patients. Because there is no theoretical reason why this should be so, these results will require confirmation from a double-blind study in a larger sample. No significant difference was observed in the subjective drug attitude between the two groups. The original hypothesis that RIS-OS shows an earlier onset of efficacy or less adverse events than RIS-ST was not supported in this study. Subsequent studies should carefully establish the differences among various forms of antipsychotic drugs.

1. Introduction

The administration of risperidone oral solution (RIS-OS) has been reported to be excellent for alleviating agitation in schizophrenia (Currier and Simpson, 2001). RIS-OS is therefore widely used in emergency care in psychiatric departments or to alleviate rapidly exacerbating symptoms. A comparison between the pharmacokinetics of RIS-OS and RIS standard tablets (RIS-ST) in Japanese subjects showed that the time required to achieve maximum plasma concentration of RIS (T_{max}) is shorter for RIS-OS (48.6 min) than for RIS-ST (67.8 min), although both forms have equal bioavailability (Risperdal Package Insert, 2002). Two studies showed that extrapyramidal symptoms decreased after replacing RIS-ST with RIS-OS as a maintenance drug (Kobayakawa et al., 2008; Uemura et al., 2006). Similarly, it was reported that intravenous haloperidol reduced extrapyramidal symptoms to a greater extent than oral haloperidol (Menza et al., 1987). Although the mechanism underlying this effect is unknown, rapid increase in the serum concentration of antipsychotic drugs may be related to decrease in the extrapyramidal symptoms.

Abbreviations: DAI, Drug Attitude Inventory; DIEPSS, Drug-Induced Extrapyramidal Symptom Scale; EUFEST, the European First Episode Schizophrenia Trial; 9-OH-RIS, 9-hydroxy-risperidone; PANSS, Positive and Negative Syndrome Scale; PANSS-EC, Positive and Negative Syndrome Scale- excited component; RIS, risperidone; RIS-FG, risperidone fine granules; RIS-OS, risperidone oral solution; RIS-ST, risperidone standard tablet.

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doi:10.1016/j.pnpbp.2010.12.010

In this study, we aimed to clarify whether RIS-OS showed a faster onset of efficacy and less adverse events, including extrapyramidal symptoms and hyperprolactinemia, than RIS-ST. We directly compared the effectiveness of RIS-OS and RIS-ST in patients with acute phase of schizophrenia in an open-label, multicentre, randomized, flexible-dose study.

2. Methods

2.1. Subjects

The subjects included 82 patients who fulfilled the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, criteria for schizophrenia. They were newly treated or had exacerbated psychotic symptoms with or without the discontinuation of antipsychotic treatments except RIS. All participants (or their legal representatives) provided written informed consent after receiving a full explanation of the study procedures.

2.2. Study design

This study was conducted at the Department of Psychiatry, Hokkaido University Hospital and its 17 associated hospitals (7 public general hospitals and 10 private psychiatric hospitals) in Hokkaido district from October 2006 to October 2008. The study protocol was approved by the institutional review board of Hokkaido University Hospital.

Patients were randomly assigned to receive RIS-OS or RIS-ST by means of sealed envelopes. Initial dose and dose titration of the two forms were at the discretion of the treating psychiatrists, after considering dose equivalency of the previous antipsychotic treatment. Subjects were treated with RIS-OS or RIS-ST once a day at bedtime. Undiluted RIS-OS was administered. Use of benzodiazepines was allowed and documented. Use of anticholinergic drugs was not allowed, unless necessitated by the appearance of acute extrapyramidal symptoms.

2.3. Assessments

Efficacy outcomes were determined using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1991), PANSS-Excited Component (EC) (Currier and Simpson, 2001), and the Drug Attitude Inventory (DAI)-30 (Hogan et al., 1983). PANSS was carried out at the baseline and at weeks 4, 8, 16, and 24 or at the last visit before discontinuation of therapy. PANSS-EC, a 5-item scale (excitement, hostility, tension, uncooperativeness, and poor impulse control) with each item scored from 1 to 7, was used to assess the acute effect of the drug on agitation and psychotic symptoms at the baseline, day 3, and weeks 1, 2, and 4. DAI-30, a self-report predictive of drug compliance, was used to evaluate subjective experience regarding the two forms of RIS at the baseline and at weeks 4 and 24.

Safety and tolerability outcomes were determined on the basis of serum prolactin level and the Drug-Induced Extrapyramidal Symptom Scale (DIEPSS), which is used to evaluate parkinsonisms, akathisia, dystonia, and dyskinesia (Inada, 1996). The DIEPSS score was evaluated at the baseline and at day 3, weeks 1, 2, 4, 8, 16, and 24 or at the time of discontinuation of the assigned drug. The serum prolactin level (measured between 6 and 9 AM) was measured at the baseline and at weeks 4, 8, 16, and 24 or at the time of discontinuation.

2.4. Data analysis

In the case of missing data, the last observation carried forward method was used. In continuous data, the repeated-measure analysis of variance was used to compare the difference for the following variables: PANSS-total and PANSS-EC scores, DIEPSS score, serum prolactin level, and dosage of coadministrated benzodiazepines. Mann–Whitney U-test was used for the following variables: the proportion of patients who needed high-dose of RIS, or who required anticholinergic drugs, and DAI-30 score. A log-rank test was used for comparing the accumulated response ratio between the groups. A student's t test was achieved for the other continuous variables. In categorical data, Fisher's exact test was used to determine between-group differences. All results are expressed as means and standard deviations. All statistical tests were two-tailed, with the significance level set at $P<0.05$.

3. Results

A total of 82 patients were enrolled in the study, of whom 44 were assigned to the RIS-OS group and 38 were assigned to the RIS-ST group. One patient in the RIS-ST group was excluded from the study just after baseline assessment because he was transferred to another hospital for the treatment of hepatitis. The remaining 81 patients completed all the baseline assessments and analyses. Seven patients dropped out during the study: 5 from the RIS-OS group and 2 from the RIS-ST group. The reasons for dropping out were patient's decision ($N=4$) and deterioration of psychotic symptoms ($N=1$) in the RIS-OS group, and extrapyramidal symptoms ($N=1$) and deterioration of psychotic symptoms ($N=1$) in the RIS-ST group. Demographic characteristics were not significantly different between the treatment groups (Table 1). There were 19 and 10 drug-free patients before enrollment of this study in RIS-OS and RIS-ST groups, respectively (Table 1). Between the two drug-free patient groups, no significant differences were observed in baseline characteristics (53% and 50% for% male, $P=1.0$; 39.4 ± 14.9 years and 45.6 ± 15.7 years for age, $P=0.31$; 1.1 ± 1.2 years and 0.8 ± 0.8 years for duration of illness, $P=0.59$; in RIS-OS and RIS-ST, respectively). The mean doses of RIS-OS and RIS-ST were not significantly different at any visits (3.2 ± 1.9 mg and 3.3 ± 1.5 mg at baseline, $P=0.68$; 4.0 ± 2.2 mg and 3.4 ± 1.6 mg at 4 weeks, $P=0.21$; 3.5 ± 2.3 mg and 3.5 ± 1.7 mg at 8 weeks, $P=0.93$; 3.4 ± 2.3 mg and 3.8 ± 2.0 mg at 16 weeks, $P=0.47$; and 3.7 ± 2.2 mg and 3.7 ± 2.0 mg at 24 weeks, $P=0.95$, respectively). The proportion of patients who needed high-dose (6 mg and more) of RIS was not significantly different between the groups (34% for RIS-OS and 24% for RIS-ST, $P=0.34$).

For the PANSS-total and PANSS-EC scores, there was a significant time effect ($P<0.001$ and $P<0.001$, respectively), but not a group effect ($P=0.47$ and $P=0.15$) or a group x time interaction ($P=0.82$ and $P=0.70$) (Table 2). In order to examine whether RIS-OS shows a faster onset of efficacy than RIS-ST, we compared the accumulated response ratio between the two groups. Treatment response was defined as 30% and more decrease in PANSS-EC score. As a result, there was no statistically significant difference in the accumulated response ratio between the two forms although RIS-OS showed a tendency towards higher response ratio than RIS-ST (19.0% and 10.8% at day 3; 40.5% and 24.7% at week 1; 57.8% and 36.3% at week 2; 60.5% and 39.2% at week 4, respectively: $P=0.06$). With regard to the extrapyramidal symptoms and serum prolactin level, data were

Table 1
Baseline characteristics of patients.

	RIS-OS	RIS-ST	P value
Number	44	37	
Male/Female	15/29	20/17	0.08
Inpatient/Outpatient	23/21	26/11	0.12
Age (y)	46.3 ± 16.6	47.5 ± 17.1	0.76
Duration of illness (y)	17.9 ± 14.2	20.4 ± 14.3	0.45
Antipsychotics before enrollment Chlorpromazine equivalent (mg)	362 ± 248	421 ± 435	0.56
Drug free before entry	19 (43.2%)	10 (27.0%)	0.17
first episode	4	7	
treatment discontinuation	15	3	