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Early treatment response predicted subsequent clinical response in patients with schizophrenia taking paliperidone extended-release

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ABSTRACT

This 6-week open-labeled study investigated whether early treatment response in patients receiving paliperidone extended-release (paliperidone ER) can facilitate prediction of responses at Week 6. Patients with schizophrenia or schizoaffective disorder were administered 9 mg/day of paliperidone ER during the first 2 weeks, after which the dose was adjusted clinically. They were assessed on Days 0, 4, 7, 14, 28, and 42 by the Positive and Negative Syndrome Scale (PANSS). The serum concentrations of 9-hydroxyrisperidone were examined on Days 14 and 42. Among the 41 patients enrolled, 26 were classified as responders (≧50% improvement on total PANSS scores at Week 6). In the receiver-operator curves (ROC) analyses, the changes in total PANSS scores at Week 2 appeared to show more accurate predictability compared to Day 4 and Day 7. At Week 6, no significant correlation was observed between blood 9-hydroxyrisperidone concentration and the total score or changes of PANSS scores. The results suggest that early treatment response to paliperidone ER, particularly at Week 2, can serve as a suitable outcome predictor at Week 6. Using 9 mg/day paliperidone ER as an initial dose for schizophrenia treatment exhibited relatively favorable tolerability and feasibility.

1. Introduction

Previous treatment guidelines have recommended that clinicians monitor antipsychotic responses for at least 4–6 weeks before changing medications (National Collaborating Centre for Mental Health, 2009). However, early prediction of treatment outcomes can prevent unnecessary delays in decision making and reduce the occurrence of medication side effects. Recent studies have suggested the possibility of predicting antipsychotic responses early in the course of treatment, and this strategy has been adopted by the prescribed guidelines (Taylor et al., 2012). In meta-analysis, a more substantial improvement in psychopathology was observed during the first 2 treatment weeks than in the weeks subsequent to the first 2 treatment weeks (Agid et al., 2003). Studies examining the treatment response of first and second generation antipsychotics, such as fluphenazine (Correll et al., 2003), risperidone (Chang et al., 2006; Leucht et al., 2007), amisulpiride (Leucht et al., 2007), and zotepine (Lin et al., 2007, 2012), have also determined that using the first 2 week's treatment result to predict the fourth or sixth weeks' treatment outcomes was acceptable in terms of specificity, sensitivity, and predictive power. Clinical response has been defined by a 20% to 50% reduction in the scores of the Brief Psychiatric Rating Scale (BPRS) or Positive and Negative Syndrome Scale (PANSS) (Lin et al., 2007; Kinon et al., 2010; Schennach-Wolff et al., 2010, 2011) in the research field for schizophrenia. Recently, a reduction of more than 50% of baseline PANSS scores, instead of absolute score reduction, has been suggested to define a clinically significant improvement (i.e., response) in subjects with various severity of illness such as acutely-ill and non-refractory patients (Leucht et al., 2009).

Paliperidone extended-release (paliperidone ER) is a new psychotropic medication enabling controlled delivery of the active metabolite of risperidone (Citrome, 2012). The recommended treatment dose for schizophrenia ranges from 3 to 12 mg/day (Fowler et al., 2008; Citrome, 2012). The optimal dosing strategy remains uncertain, with a starting dose having been used as 6 mg/day (Marino and Caballero, 2008; Citrome, 2012), 9 mg/day (Kramer et al., 2010), and 12 mg/day (Canuso et al., 2010) in relevant literature. Fixed dose of paliperidone 3, 6, 9, 12 or 15 mg/day have also been used in previous clinical trials (Davidson et al., 2007; Kane et al., 2007; Marder et al., 2007). These earlier 6-week trials

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suggested that fixed dose of 9 mg/day paliperidone ER, compared to 6 mg/day, has a greater completion rate (66% vs. 56%) and lower or similar dropout rate (4% vs. 7%) despite higher extrapyramidal adverse effects (25% vs. 10%) (Meltzer et al., 2008). Furthermore, the only one study using 9 mg/day as the starting dose enrolled patients with stable condition (Kramer et al., 2010). In this study, we would like to test whether 9 mg/day paliperidone would be a feasible starting dose for patients in acute exacerbation.

Remarkably, a significant improvement in the total PANSS scores has been observed on the fourth day of paliperidone ER administration in most trials (Davidson et al., 2007; Chwieduk and Keating, 2010). One recent report has shown that paliperidone ER treatment response at Week 6 could be predicted by an early response at Week 2 in hospitalized schizophrenia patients (Heres et al., 2014). However, the study was based on secondary analyses of clinical trial data which had also included subjects taking concomitant treatment with other antipsychotics and tested specifically the predictability of the Week-2 response. Whether an even earlier prediction model can be applied to Day 4 or 7 drug response remains to be determined. Previously, Riedel et al. (2005) observed a correlation between active moiety plasma levels of risperidone (risperidone plus 9-hydroxyrisperidone) and clinical responses in patients receiving risperidone treatment. In addition, despite using similar doses, the responders to risperidone treatment have been shown to exhibit significantly lower active moiety plasma levels of risperidone than did the nonresponders (Riedel et al., 2005). Paliperidone (9-hydroxyrisperidone), as a metabolite of risperidone, has similar but not identical, pharmacology and pharmacokinetics (Chue et al., 2012; Suzuki et al., 2014; Corena-McLeod, 2015). Current data on the relationship between the plasma level of paliperidone and its clinical effects after paliperidone ER treatment (Suzuki et al., 2014) are relatively fewer than that of risperidone (Lopez and Kane, 2013). Moreover, the plasma concentrations of risperidone in Taiwanese patients have been reported to be higher than those of Caucasian patients (Lai et al., 2009), suggesting a possible ethnic difference in the drug metabolism of paliperidone.

The aim of this 6-week open-labeled study was to investigate whether early symptom improvement in PANSS score reduction on Days 4, Day 7, or Day 14 after paliperidone ER treatment in patients with schizophrenia can predict their ultimate clinical response at Week 6. This study also tested whether the starting dosage of 9 mg/day of paliperidone ER was feasible in the schizophrenia patients with acute exacerbation, and evaluated the associations of paliperidone levels with clinical responses as well as adverse effects at Week 6.

2. Methods

This study was conducted at the Taipei City Psychiatric Center, Taipei City Hospital, Taiwan. It was approved by the Institutional Review Board of Taipei City Hospital before case enrollment and registered on www.clincaltrials.gov (NCT02075528).

2.1. Participants

Eligible patients admitted to an acute psychiatric ward were screened and evaluated by the researchers. Written informed consent was obtained from patients before participation. The ability to provide informed consent was first evaluated by psychiatrists other than the researchers.

The inclusion criteria were: (1) age between 18 and 65 years, (2) diagnosis of schizophrenia or schizoaffective disorder according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV), (3) baseline total PANSS score≧60 (Chang et al., 2006; Canuso et al., 2010), (4) not having received long-acting antipsychotic injections in the preceding 6 months, and (5) no major systemic illnesses based on physical examinations and laboratory test results. The exclusion criteria were: (1) diagnoses of substance (except nicotine) dependence in the previous 6 months, (2) a medical condition that could affect absorption, metabolism, or excretion of the study drug, (3) substantial risks of suicide or violent behavior, (4) pregnancy or breastfeeding, (5) documented organic diseases of the central nervous system, (6) unstable or critical untreated medical illness, (7) history of clozapine treatment in the previous 3 months, and (8) participation in an investigational drug trial in the 30 days before screening.

2.2. Study design

The participants were assigned to receive a fixed dosage of 9 mg/day of paliperidone ER for the first 2 weeks. The paliperidone ER dosage was adjusted flexibly after 2 weeks according to the clinical judgment of the physicians in charge. The patients were allowed to use lorazepam (maximum of 4 mg/day) for insomnia or agitation, and benztropine (maximum of 6 mg/day) for managing extrapyramidal side effects. No other psychotropic agents were used during the 6-week study. The compliance and safety of participants were monitored by the research psychiatrists.

The efficacy and safety of drug were assessed by experienced researchers on Days 0, 4, 7, 14, 28, and 42. Efficacy was measured using the PANSS, Personal and Social Performance Scale (PSP) (Wu et al., 2013), and Clinical Global Impression-Severity (CGI-S). Drug safety was evaluated using routine physical and neurological examinations, laboratory tests, the Drug-Induced Extrapyramidal Symptom Scale (DIEPSS) (Kim et al., 2002; Knol et al., 2010) and the Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating Scale (Knol et al., 2010). Any new event or worsening of an existing condition that required concomitant therapy to be administered as treatment was documented on an adverse-event form. Serum concentrations of 9-hydroxyrisperidone were assessed on Days 14 and 42. Venous blood was collected into an EDTA-tube and centrifuged at 3000 rpm for 15 minutes. The plasma samples were stored at −80 °C until they were assayed. Determinations of risperidone and 9-hydroxyrisperidone levels were performed using high-performance liquid chromatography (HPLC) and ultraviolet detection. The lower limit of quantification (LLQ) of HPLC was 5 ng/dL. Detailed procedures have been described elsewhere (Lai et al., 2009).

2.3. Statistical analysis

The primary endpoint was set for identifying responders and nonresponders. Responders were defined as those patients who exhibited a reduction of 50% or more in total PANSS scores after 6 weeks' treatment. The percentage of total PANSS score reduction was calculated as $(PANSS_{baseline} - PANSS_{endpoint}/PANSS_{basline} - 30)$ *100% (Leucht et al., 2009). The secondary endpoints were set for documenting changes in other clinical measurements (PANSS, CGI, PSP, DIEPSS, and UKU), and serum concentrations of 9-hydroxyrisperidone at Week 6.

At Week 6, responders and nonresponders were initially compared regarding demographic data, age of onset, and total baseline PANSS scores and subscores at Days 4, 7, and 14. The Pearson χ^2 test or Fisher exact test were used to compare categorical variables, and an independent t test was conducted for continuous variables. The last-observation-carry-forward (LOCF) method for the clinical rating data was applied in the analysis to provide a conservative estimate for the dropouts.

We used receiver operating characteristic (ROC) analysis