Proposal No: 100-046

Title:

Differences in Lipid and Cognitive change between one-month and 3-month Paliperidone Palmitate treatment in stable schizophrenia

Study institution: Calo Psychiatric Center, Pintung County, Taiwan

Study period: January 01, 2015 to June 30, 2017

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The study will approved by the Institutional Review Board at Kaohsiung Armed Forces General Hospital (IRB-100046) in Taiwan.

Abstract

Schizophrenia is a chronic and severe psychiatric disorder, these patients suffer from positive symptoms, negative symptoms and cognitive deficits, of which working memory problems are considered a central cognitive impairment. Atypical antipsychotics are believed to have a superior effect in reducing both positive and negative symptoms of schizophrenia, coupled with a low risk of extrapyramidal symptoms. Particularly, 2nd-generation antipsychotic medications are commonly used in treatment of schizophrenia. An antipsychotic drug, Paliperidone palmitate (PDP), is administered to patients with schizophrenia as injections at one-month (PP1M) or three-month (PP3M) intervals. This study was compare the effects of treatment, social function, and side effects between PP1M and PP3M in patients with schizophrenia. Moreover, the changes of cognitive and lipid profile between two PDP were also explored. Firstly, participants were received the one month long-acting injection (PP1M) three months. Then, the stable participants were shifted to the three month long-acting injection (PP3M). Concomitant medications were allowed to prescribe except other antipsychotics. Outcome measurements were 20-item Toronto Alexithymia Scale (TAS-20), 45-itme quality of life for mental disorder (QOLMD), Short-version of the Udvalg for Kliniske Undersogelser (short-version UKU), and Wisconsin Card Sorting test (WCST). These measurements were performed every three-month except WCST which was performed every six-month. The different effects of PP1M and PP3M will be expected to find out in this study.

Key words: paliperidone palmitate, social function, cognitive function, quality of life

Abbreviations

PDP: Paliperidone palmitate

PP1M: one month long-acting injection

PP3M: three month long-acting injection

TAS-20: 20-item Toronto Alexithymia Scale

QOLMD: 45-itme quality of life for mental disorder

UKU: Udvalg for Kliniske Undersogelser scales

WCST: Wisconsin Card Sorting test

PSP: Personal and Social Performance scales

TC: total cholesterol

TG: Triglyceride

HDL: High-density Lipoprotein

LDL: Low-density Lipoprotein

GEE-I: Generalized Estimating Equations-I

SEM: structural equation model

AGFI: adjusted goodness-of-fit index)

RMSEA: root mean square error of approximation

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition

Introduction

Schizophrenia is a chronic and severe psychiatric disorder, these patients suffer from positive symptoms, negative symptoms and cognitive deficits, of which working memory problems are considered a central cognitive impairment [1-5]. Atypical antipsychotics are believed to have a superior effect in reducing both positive and negative symptoms of schizophrenia, coupled with a low risk of extrapyramidal symptoms [6]. Particularly, 2nd-generation antipsychotic medications are commonly used in treatment of schizophrenia [7]. Second-generation antipsychotics have reducing the incidence and severity of side-effect from 1st-generation antipsychotics, however, 2nd-generation antipsychotics may induce cardiovascular and metabolic abnormalities (such as obesity, hyperglycemia, dyslipidemia and the metabolic syndrome) that are associated with an increased risk of type 2 diabetes mellitus and cardiovascular disease [8-10].

In fact, one of major problem for patients with schizophrenia is non-adherence with maintenance treatment, hence, the depot antipsychotics have been developing. Long-acting injections (LAIs) were administering only once every 2-4 weeks rather than each day for addressing the problem of noncompliance [10]. Despite intuitive assumptions that LAIs will bring the superior compliance rates comparing with oral antipsychotics for patients with schizophrenia. Several studies have found no differences in compliance rates between oral and injecting antipsychotics [11,12]. However, several studies have found, LAIs can led to lower rates of noncompliance and re-hospitalization than oral antipsychotics [13-15]. Overall, the previous studies have demonstrated LAIs are as safe and effective treatment in schizophrenia as oral antipsychotics, particularly 2nd-generation LAIs [10-15].

Paliperidone palmitate (PDP), is a LAIs of the atypical antipsychotic

paliperidone, the primary active metabolite of risperidone. Comparing with other LAIs, PDP is able to more rapidly achieve steady stat and maintain this steady state of longer period of time [10]. PDP has been found that its efficacy with more safety and tolerability, better cost–benefit ratio, lower withdrawal rate, incidence of relapse and weight gain than other atypical antipsychotics [16,17], and the pharmacokinetic characteristics are similar in different ethnic people [18]. The standard dosing schedule is induction therapy with maintenance dose every 4 weeks (PP1M) or 12 weeks (PP3M). However, the differences between PP1M and PP3M still remain unknown.

Hence, the aim of this study was to compare the effects of treatment and side effects between PP1M and PP3M in patients with schizophrenia. Moreover, the changes of cognitive and lipid profile between two kinds of PDP were also explored. Furthermore, the psychological function and performance, and quality of life would be investigated in this study.

Methods

The study will approved by the Institutional Review Board at Kaohsiung Armed Forces General Hospital (IRB-100046) in Taiwan, and following an explanation, written informed consents are obtained either directly form the patients or from their legal guardians. All participants will notified that they could withdraw at anytime.

Study design

This is a two and half-one years, single-arm, nonrandomized, open-label study which will conducted between Jan 2015 to Jun 2017 including from a psychiatric center in southern Taiwan. The stable schizophrenic patients who previously received

risperidone long-acting injection for more than one year and shifted to paliperidone palmitate after including in the study. Firstly, participants will received the one month long-acting injection (PP1M) three months. Then, the stable participants will shifted to the three month long-acting injection (PP3M). Concomitant medications will allowed to prescribe except other antipsychotics. Outcome measurements include 20-item Toronto Alexithymia Scale (TAS-20), 45-itme quality of life for mental disorder (QOLMD), Short-version of the Udvalg for Kliniske Undersogelser (short-version UKU), and Wisconsin Card Sorting test (WCST). These measurements will performed every three-month except WCST which was performed every six-month. The effect of treatment will assessed using Personal and Social Performance (PSP) scales [19,20] for the evaluation of psychosocial functioning at 0, 4, 8, and 12 weeks in first study, and at 0, 3, 6, 9, 12 months in second study, respectively. In addition, all participants will assessed for body weight, waist circumference, and blood lipid profile. To evaluate the lipid profiles, fasting blood samples were analyzed for total cholesterol (TC), Triglyceride (TG), High-density Lipoprotein (HDL) and Low-density Lipoprotein (LDL). These blood samples will collected at every month until study completion.

Participants

Total of 72 participants, including 41men and 31 female, will recruited in the PP1M three months. The stable participants will shifted to PP3M. Patients who had comorbid serious medical illnesses, and may therefore present substantial clinical risk due to pharmacotherapy, were excluded from the sample, as were pregnant and lactating women. All of them had to meet the diagnostic criteria for schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)

[21].

Assessment tools

20-item Toronto Alexithymia Scale (TAS-20)

The traditional Chinese-language version of the 20-item TAS was validated in a Taiwanese student population by Lin and Chan [22]. The TAS scores were calculated for three sub-factors: 1) difficulty identifying feelings (DIF), 2) difficulty describing feelings (DDF), and 3) externally-oriented thinking (EOT). The 20 items are rated from 1 (strongly disagree) to 5 (strongly agree). The sum of all 20 items, taking reversed items into account, was used to generate a TAS total score. Those scoring greater or equal to 61 is considered alexithymia (high in alexithymia) [23].

45-item Quality of Life for Mental Disorders (QOLMD)

The QOLMD health survey measures HRQOL, and was revised based on the Quality of Life Interview Scale (QOLIS) with 87 items and Quality of Life Scale (QLS) [24] with 21 items. The QOLMD contains 45 items with eight dimensions, including 7 items of life satisfaction, 7 items of autonomy, 6 items of health maintenance, 5 items of family support, 5 items of economic ability, 7 items of social activities, 4 items of physical health, and 4 items of mental health, rated from 0 to 3. The internal consistency of the eight dimensions of the QOLMD was Cronbach's alpha .58-.84, and the corrected item-total correlations were Pearson's r >.30 [25]. A higher score represents better health status.

Short-version of the Udvalg for Kliniske Undersogelser (short-version UKU)

The nine items in the UKU-short were selected from those having high patient-doctor reliability (p less than 0.01) [26], with the addition of the four symptoms of somnolence, insomnia, dry mouth and dizziness, which were found to

occur in co-administration of antipsychotics [27], and the deletion of the sexual dysfunction item. The selection process resulted in the two items of sedation and reduced sleep in the psychic side effect dimension, the four items of rigidity, tremor, akathisia and headache in the neurological side effects dimension, and the three items of reduced salivation, constipation and orthostatic dizziness in the autonomic side effects dimension. The procedure for the using the short version is the same as that for the original UKU [28], except each item is defined by means of a 2-point-scale (0-1). In general, 0 means "not or doubtfully present", and 1 indicates that a symptom is present to a mild or severe degree. The Chinese version of UKU presented good reliability and validity [29]

Wisconsin Card Sorting Test (WCST)

The computerized version of the WCST was developed based on the standardized criteria of Heaton, Chelune, Talley, Kay, & Curtiss [30] by Tien et al [31]. According to Heaton's criteria [30], response results should be interpreted based on categories achieved, percent of perseverative errors and non-perseverative errors, percent of total errors, trials to complete the first category, conceptual level response, failure to maintain set, and learning-to-learn indices. The performance of cognitive function will be intend to examine at first week before receiving cassia obtusifolia as baseline. Then, we examine the cognitive function at month 12 in first, second and third year.

Statistical Analysis

Data were analyzed using the SPSS 21.0 for Windows software package and subject to demographic analysis and descriptive analysis. This study used a monotherapy design in two different antipsychotics treatment, and applied the

Generalized Estimating Equations-I (GEE-I), developed by Liang and Zeger in 1986 [32].

AMOS for Windows 21.0 was used to apply a structural equation model (SEM) and to construct several theoretical models of variables analyzed in this study. SEM uses the χ^2 fit test to investigate the overall fit of the hypothesized models; χ^2 values resulting in $p > 0.05$ and an adjusted goodness-of-fit index (AGFI) > 0.9 indicated that the model described the observed data adequately. The root mean square error of approximation (RMSEA) is based upon the non-centrality parameter. Good models using SEM supposedly have an RMSEA ≤ 0.05; however, models with an RMSEA of 0.10 or less are also acceptable [33].

Expectation

- To find out the different treatment effects between PP1M and PP3M in patients with schizophrenia.
- To find out the different side effects between PP1M and PP3M in patients with schizophrenia.
- To investigate the differences of cognitive performance, and lipid profile between PP1M and PP3M in patients with schizophrenia.
- To explore the differences of psychological function and performance, and quality of life between PP1M and PP3M in patients with schizophrenia.

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