

PALIPERIDONE ER: A NEW TREATMENT FOR SCHIZOPHRENIA

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Abstrak. Generasi kedua antipsikotik untuk pengobatan skizofrenia telah ditemukan. Paliperidone ER (InvegaTM) telah disetujui pada tahun 2007 oleh Badan Pengawas Obat dan Makanan Amerika untuk mengobati pasien dengan skizofrenia. Formulasi Paliperidone ER yang menggunakan Alza OROS (Osmotic-controlled Release Oral-delivery System) dan menggunakan tekanan osmotik melepaskan pengobatan dalam tingkatan plasma darah yang ringan. Beberapa studi yang disponsori oleh Johnson dan Johnson Pharmaceutical Research and Development menemukan bahwa semua dosis Paliperidone ER efektif dalam mengontrol sejumlah besar simptom skizofrenia dan fungsi personal dan sosial pasien serta umumnya dapat ditoleransi dengan baik. (JKS 2013; 3: 159-165)

Kata kunci : skizofrenia, paliperidone, efektif

Abstract. A new second-generation antipsychotic for the treatment of schizophrenia has been found. Paliperidone ER (InvegaTM) was approved in 2007 by Food and Drug Administration (FDA) to treat patients with schizophrenia. The formulation of Paliperidone ER by using the Alza OROS (Osmotic-controlled Release Oral-delivery System) and utilizing osmotic pressure release medication in smooth blood plasma levels. Several studies that were sponsored by Johnson and Johnson Pharmaceutical Research and Development found that all doses of paliperidone ER is effective in controlling a broad range of the symptoms of schizophrenia and personal and social functioning and generally well tolerated. (JKS 2013; 3: 159-165)

Key words : schizophrenia, paliperidone, effective

Introduction

Schizophrenia is one of the most serious mental health problems faced by people today. Schizophrenia is a disease that lasts about six months, and in the first month, the active-phase symptoms, such as delusions, hallucinations, disorganized speech, and catatonic behavior will occur.¹ Based on over 20,000 household interviews, the National Institute of Mental Health Epidemiology Catchments Area Study (ECA) found that roughly 1.5 percent of the United States population met criteria for a life-time diagnosis of schizophrenia” (p.35)² In addition, approximately 2.4 million American adults or about 1.1 percent of the population age 18 and older in a given year have schizophrenia. Schizophrenia affects men and women with equal frequency (p.3).³

Antipsychotic medications have become cornerstone to treat schizophrenia. Some antipsychotic drugs, such as olanzapine, perphenazine, quetiapine, risperidone are effective to treat schizophrenia patients even though they have side effects.⁴ In 2007, the United States Food and Drug Administration (FDA) approved InvegaTM (paliperidone Extended-Release) tablets for short term and long-term treatment of schizophrenia. The approval of paliperidone for schizophrenia was “based on a long-term efficacy study that demonstrated a significant benefit in delaying the time to relapse of symptoms of schizophrenia”. The study also supported the safety and tolerability profile when it was conducted in prior short-term studies.⁵

This manuscript reviews several studies that were conducted to measure the efficacy and safety of paliperidone ER for schizophrenia patients. Because paliperidone ER is so new drug, most of the studies examined the efficacy, safety,

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and tolerability of paliperidone ER in treating patients with schizophrenia. The studies were conducted not only in the United States, but also in some centers in Canada, Mexico, Europe, Asia, Israel and Africa.

Paliperidone and Schizophrenia

Paliperidone ER is a new atypical antipsychotic drug for the treatment of schizophrenia. Paliperidone ER is “an active metabolite of risperidone (9-OH risperidone) and show almost the same pharmacological profile, with high affinity for dopamine D₂ receptor and serotonin 5-HT₂ receptor” (p.1).⁶ The Alza OROS technology delivery system and utilizing osmotic pressure were used to formulate paliperidone ER.⁷ “The technology is designed to release medication in a unique design pattern over a 24-hour period, leading to smooth blood plasma levels” (Medical News Today, p.2). Paliperidone ER has similar effect to its parent compound (risperidone). Paliperidone ER likely has lower risk because it is metabolized less by the liver.⁸

Davidson, Emsley, Kramer, Ford, Pan, Lim and Eerdeken (2007)

Davidson et al examined the efficacy, safety, and effect on personal and social functioning of three fixed doses of once-daily paliperidone ER (3 mg, 9 mg, and 15 mg) compared with placebo in 618 patients who were experiencing severe schizophrenia. This study was conducted between May 2004 and May 2005 at 74 centers: 31 centers in North America and Canada, 17 in Eastern Europe, 12 in Asia, 5 in Israel, 5 in Mexico, and 4 in South Africa.⁹

Design and Participants

This was a double-blind, randomized, placebo-and active controlled, parallel group, dose-response study of once-daily paliperidone ER (3 mg, 9 mg, and 15 mg), conducted at multicenter and lasting for six weeks. A number of 618 patients, male or female, aged 18 and older, with a

Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnosed schizophrenia and had total score of Positive and Negative Syndrome Scale (PANSS) between 70 and 120 were involved in the study.

In this study, patients who didn't meet the inclusion criteria were refused. Exclusion criteria included a diagnosis of substance dependence, medical condition that could affect absorption, metabolism, or excretion of the study drug, history of tardive dyskinesia, being at significant risk for suicide, pregnant women, and women who were breastfeeding, patients who were receiving antipsychotic within 120 days, and patients who were using antidepressant within two weeks before the screening.

During a 5-day screening, patients who met the inclusion or exclusion criteria stopped prior medications, such as antipsychotic medication, antiparkinson drugs, beta blockers and prescription, herbal or over-the-counter- psychotropics. Pre-defined doses of benzodiazepines and antidepressants were permitted as rescue medication. “Eligible patients were assigned to receive fixed oral dosages of paliperidone ER 3 mg, 9 mg, 15 mg, placebo or olanzapine 10 mg once daily in the morning for six weeks (Day 43 = end point)” (pg. 120). The purpose to include the olanzapine group was to provide an adequate parallel active control group in case there was negative result for paliperidone ER compared with placebo.

The change in Positive and Negative Syndrome Scale (PANSS) total score for each dose of paliperidone ER compared with placebo was used to measure the primary efficacy end point (from baseline to Days 43). The change in Clinical and Global Impression Scale-Severity (CGI-S) scores and Personal and Social Performance (PSP) scale were used to measure secondary efficacy endpoints (from baseline to endpoints). Other efficacy endpoints used were the change from baseline to endpoints in PANSS Marder factor scores, assessment of the

onset of therapeutic effect and determination of clinical response.

The safety assessments included Adverse Events (AEs), treatment-emergent glucose, prolactin, and extra-pyramidal symptoms (EPS) related AEs (TEAEs), the Abnormal Involuntary Movement Scale (AIMS), the Barnes Akathisia Rating Scale (BARS), The Simpson-Angus Rating Scale (SAS), and clinical laboratory evaluations.

Analysis and Results

To analyze PANSS total and factor scores and change on CGI-S and PSP scale score from baseline to endpoint, the analysis of covariance (ANCOVA) was used. Analysis of variance (ANOVA) was used for safety analyses.

A number of 618 patients were screened and randomized. Only 605 patients were included in the intent-to-treat (ITT) group. 120 patients were randomized to placebo, 123 patients to paliperidone ER 3 mg, 123 patients to paliperidone ER 9 mg, 113 patients to paliperidone ER 15 mg and 126 to olanzapine 10 mg.

In this study, of the 618 patients, only 59 percent completed 6-week study. Lack of efficacy with the highest rate in the placebo control was the primary reason why early withdrawal occurred. The low and comparable of AEs (TEAEs) score were the reason why the patients discontinuing treatment from the study.

For the efficacy results, the total score of PANSS was significantly greater in all paliperidone ER treatment groups ($p < 0.001$) than in the placebo group. PANSS Marder factor scores showed statistically significant progress of paliperidone ER 3 mg, 9 mg, and 15 mg over the placebo ($p \leq 0.005$). This progress improved from the first observation point (Day 4) to the end of the double-blind phase. The progress also occurred in mean PSP scale scores from baseline to endpoint for all three doses paliperidone ER 3 mg, 9 mg, and 15 mg versus placebo ($p \leq 0.001$).

On the CGI-S scale for patients treated with all doses of paliperidone ER compared with placebo, the significant

improvement also occurred at end point ($p < 0.001$). Only a few patients were classified as “marked” or “severely ill” on the CGIS-S scale at end point.

There was no obvious dose-response relationship for the severity of TEAEs observed with paliperidone ER. Insomnia, headache, and tachycardia were often reported by all groups. Also in all treatment groups, the rate of serious TEAEs was low.

For the Barnes Akathisia Rating Scale clinical global score at end point, the differences between the paliperidone ER groups and placebo were not found. Also there was no significant difference between placebo and paliperidone ER groups in AIMS total score. The median total AIMS score was zero.

Discussion

The study demonstrated that all doses of Paliperidone ER (3 mg, 9 mg and 15 mg) were effective than placebo in improving symptoms of schizophrenia as shown in the change of PANSS total and CGI-S scores from baseline. In addition, the Marder factor symptoms scores showed that paliperidone EP significantly improved the symptoms domain compared with placebo.

The study emphasized that paliperidone ER was effective at all doses. However, by considering all efficacy and safety data from different studies, the recommended dose range for paliperidone was 3 – 12 mg. Paliperidone ER was well tolerated for schizophrenia patients without significant changes in the majority of lipid parameters and weight gain (< 2 kg).

Limitation

The short time period (six weeks) is considered as the limitation of this study. Therefore, the long term period to measure the efficacy and tolerability data of paliperidone ER for schizophrenia patients is needed to prevent recurrence. Another limitation of the study cited by the authors was the differences of the number of previous hospitalization for each patient

between the groups. About 25 % of the subjects in the 3 mg dose group had ≥ 4 hospitalizations compared to placebo group (29%), 9 mg dose group (28%), 15 mg dose group (32%), and olanzapine (36%). The authors cited that the efficacy results for the paliperidone ER 3 mg might be not completely comparable with other doses of paliperidone ER.

Kane, Canas, Kramer, Ford, Mayer, Lim, and Eerdeken (2007)

Kane et al. examined the efficacy and safety of once-daily paliperidone ER (6 mg, 9 mg, and 12 mg) for the treatment of schizophrenia compared with placebo in 630 patients with acute schizophrenia. This study was conducted between 29 March 2004 and 25 January 2005 at 47 centers in Europe and 6 centers in India.¹⁰

Design and Participants

This was a 6-week, double-blind, multicenter, randomized, placebo-and active controlled, parallel group, dose-response study of once-daily paliperidone ER (6 mg, 9 mg, and 12 mg). A number of 630 patients, male or female, aged 18 and older, who had total score of Positive and Negative Syndrome Scale (PANSS) between 70 and 120 and were diagnosed with schizophrenia based on *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) were involved in the study.

In this study, exclusion criteria included a diagnosis of substance dependence, medical condition that could affect absorption, metabolism, or excretion of the study drug, history of tardive dyskinesia, being at significant risk for suicide, pregnant women, and women who were breastfeeding, patients who were receiving antipsychotic within 120 days or paliperidone palmitate as part of a clinical trial within 10 months before screening, and patients who were using antidepressant within two weeks before the screening.

During a 5-day screening, patients who met the criteria of inclusion or exclusion discontinued prior medications, such as

antipsychotic medication, antiparkinson drugs, beta blockers and prescription, herbal or over-the-counter- psychotropics. Permitted rescue medication included benzodiazepines and antidepressants. Only suitable patients were assigned to receive fixed oral dosages of paliperidone ER 6 mg, 9 mg, and 12 mg, placebo or olanzapine 10 mg once daily in the morning for six weeks (Day 43 = end point). Olanzapine group was only parallel active control group in case there was negative result for paliperidone ER compared with placebo.

Positive and Negative Syndrome Scale (PANSS), Clinical and Global Impression Scale-Severity (CGI-S), and Personal and Social Performance (PSP) total scores were used to measure the primary efficacy end point from baseline to Days 43. To measure safety assessments, Adverse Events (AEs), treatment-emergent AES (TEAEs), the Abnormal Involuntary Movement Scale (AIMS), the Barnes Akathisia Rating Scale (BARS), The Simpson-Angus Rating Scale (SAS), and clinical laboratory evaluations were used.

Analysis and Results

For statistical analyses of efficacy assessment, analysis of covariance (ANCOVA) was used to analyze PANSS total and factor scores and change on CGI-S and PSP scale score from baseline to endpoint. Analysis of variance (ANOVA) was used for safety analyses.

Of the 630 patients screened and randomized, 628 patients were included in the ITT group (placebo [n=126], paliperidone ER 6 mg [n=123], paliperidone ER 9 mg [n= 122], paliperidone ER 12 mg [n=129], and olanzapine [n=128])” (pg. 151). Patients who were diagnosed with paranoid schizophrenia and severed from acute symptoms had PANSS total score of 93.9 ± 11.0 . Patients who were “markedly ill” on the CGI-S scale were rated 62 % at baseline. Paliperidone ER treatment groups (for all doses) showed greater mean change

from baseline to end point compared with the placebo group ($p<0.001$).

On PANSS Marder factor scores, paliperidone ER 6 mg, 9 mg, and 12 mg showed significantly greater improvement than placebo ($p<0.001$). This progress improved from the first observation point (Day 4) for paliperidone ER 12 mg ($p<0.01$), and from Day 8 for paliperidone ER 6 mg and 9 mg groups ($p<0.05$ versus change in placebo group). Significant improvement occurred in personal and social functioning from baseline to endpoint for all paliperidone ER treatment groups compared with placebo ($p<0.001$). Significant improvement also occurred on the CGI-S scale for patients who were treated with all doses of paliperidone ER compared with placebo ($p<0.001$). About 64.1 % of patients were “marked” or “severely ill” at baseline, compared with 23 % at end point in the olanzapine group. There was no obvious dose-response relationship for the severity of TEAEs observed with paliperidone ER. The AEs reported insomnia and tachycardia often complained in all treatment groups while tachycardia, extrapyramidal disorder, and hyperkinesias were frequently reported in the paliperidone ER groups than placebo group.

Discussion

The study demonstrated that all three doses of Paliperidone ER (6 mg, 9 mg, and 12 mg) were effective than placebo in improving symptoms of schizophrenia as shown in the change of PANSS total and CGI-S scores from baseline to end point. In addition, the improvement of various aspects of personal and social functioning also recorded in the PSP scale. This study indicated that paliperidone ER was well tolerated for patients with schizophrenia and effective in controlling schizophrenia symptoms.

Limitation

Paliperidone ER was well tolerated for the treatment of schizophrenia in this study. However, to assess the efficacy and

tolerability of paliperidone ER to treat patients with schizophrenia, long term period of study is needed to get the best result.

Marder, Kramer, Ford, E. Errdekins, Lim, M. Eerdekins, and Lowy (2007)

Marder et al. studied efficacy and safety of once-daily paliperidone ER (6 mg and 12 mg) versus placebo in the treatment of 444 patients with acute schizophrenia. This study was conducted at 74 centers in the United States between 17 February 2004 and 22 December 2004.¹¹

Design and Participants

This was a 6-week, double-blind, multicenter, randomized, placebo-and active controlled, parallel group, dose-response study of once-daily paliperidone ER (6 mg and 12 mg). A number of 444 patients, male or female, aged 18 and older, with *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) diagnosed schizophrenia and had total score of Positive and Negative Syndrome Scale (PANSS) between 70 and 120 and were involved in the study.

The study employed several exclusion criteria including medical condition that could affect absorption, metabolism, or excretion of the study drug, a diagnosis of substance dependence, history of tardive dyskinesia, being at significant risk for suicide, women who were pregnant and breastfeeding, patients who were receiving antipsychotic within 120 days or paliperidone palmitate as part of a clinical trial within 10 months before screening, and patients who were using antidepressant within two weeks before the screening.

Patients who met the inclusion or exclusion criteria stopped prior medications, such as antipsychotic medication, antiparkinson drugs, beta blockers and prescription, herbal or over-the-counter-psychoactives during a 5-day screening. Only benzodiazepines and antidepressants were permitted as rescue medications. Based on a computer-

generated randomization and stratification scheme using an Interactive Voice Response System, appropriate patients were assigned to receive fixed oral dosages of paliperidone ER 6 mg or 12 mg, placebo or olanzapine 10 mg once daily in the morning for six weeks (Day 43 = end point). Olanzapine was included in the study to provide a concurrent active control group to confirm that the study was adequate to detect drug effect and not for comparative purposes.

Efficacy measures used in the study were Positive and Negative Syndrome Scale (PANSS), Clinical and Global Impression Scale-Severity (CGI-S), and Personal and Social Performance (PSP). Safety assessments used were Adverse Events (AEs), treatment-emergent AEs (TEAEs), the Abnormal Involuntary Movement Scale (AIMS), the Barnes Akathisia Rating Scale (BARS), The Simpson-Angus Rating Scale (SAS), and clinical laboratory evaluations.

Analysis and Results

Analysis of covariance (ANCOVA) was used to analyzed PANSS total and factor scores, change on CGI-S and PSP scale score from baseline to endpoint. Analysis of variance (ANOVA) was used for safety analyses. Only 43 % of the 444 patients randomized completed the 6-week study. The primary reason for early withdrawal was due to lack of efficacy with the highest rate in the placebo control. The low and comparable of AEs scores across group were the reason why the patients discontinuing treatment from the study.

In PANSS total score, mean change from baseline and endpoint was significantly greater for paliperidone ER 6 mg ($p=.006$) and 12 mg ($p<.001$) versus placebo. Paliperidone ER 6 mg and 12 mg also showed significantly progress in Marder positive factor scores ($p<.005$), Marder negative factor scores ($p=.007$ and $p=.025$, respectively). Based on comparison PSP scale score from baseline to endpoint, patients in treatment groups of paliperidone 6 mg and 12 mg showed an improvement of one or more categories compared with

placebo. Paliperidone ER 6 mg and 12 mg also showed significantly progress over placebo on the CGI-S scale.

Headache, somnolence, insomnia, and dyspepsia were commonly reported in all groups. "Headache was the most frequently reported AE among patients who received paliperidone ER (24%) compared with placebo (19%)" (p. 1366). Patients in the group of paliperidone ER 12 mg mostly reported hypertonia (6%), dystonia (4%), tongue paralysis (2%), and hyperkinesias (9%).

There were no significant differences of change from baseline to endpoint between paliperidone ER and placebo in SAS global scores. For the BARS global clinical score, the differences between the paliperidone ER groups and placebo were found at day 43 ($p=.001$). The median total AIMS score was zero (no symptoms) at baseline and endpoint in all groups.

Discussion

Paliperidone ER 6 mg and 12 mg were effective compared with placebo for the treatment of patients with schizophrenia. Based on PANSS factor scores, paliperidone ER 6 mg and 12 mg demonstrated wide range efficacy, improving positive, negative, uncontrolled hostility, and excitement symptoms of schizophrenia. Paliperidone 12 mg demonstrated significant improvement over placebo in disorganized thought. Based on PSP scale, patients treated with paliperidone ER showed improvement in patient functioning.

Limitation

This study was conducted in a short time period (six weeks). The results only showed short term effect on paliperidone ER. Thus, long term study is needed to get maximal result on efficacy, safety, and tolerability of paliperidone ER.

Commentary

The studies that were conducted to assess the efficacy, safety, and tolerability of paliperidone to treat patients with

schizophrenia were sponsored by Johnson & Johnson Pharmaceutical Research and Development, L.L.C. Because paliperidone ER is a new medication that was released on 2007, the research about this drug is very limited. The three studies only repeat the same method in a short term period (6 weeks). It is the time for the sponsor to try to conduct a long term period research to assess the efficacy, safety, and tolerability of paliperidone ER. The result from short term studies is not adequate to generalize the efficacy of paliperidone ER. Maybe other surprising effects will be found if paliperidone ER was conducted in a long term period.

The uniqueness of paliperidone ER that is formulated using OROS technology delivery system might attract physicians to prescribe this medication as an alternative to treat patients with schizophrenia. In addition, the result of the studies that demonstrated the effectiveness of paliperidone ER to improve personal and social functioning of schizophrenia patients is very promising.

Conceptualization

The three studies demonstrated the similar results that paliperidone ER was effective in improving the symptoms of schizophrenia and personal and social functioning patients with schizophrenia. The studies showed similar positive results about efficacy, safety, and tolerability of paliperidone ER. The studies also found that paliperidone ER has common adverse reactions for patients such as, insomnia, headache, and tachycardia. Nevertheless, compared with placebo or olanzapine, paliperidone ER has much superiority. This superiority perhaps will lead paliperidone ER to be the best choice for the treatment of schizophrenia.

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