Paliperidone ER: a review of the clinical trial data

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Abstract: Paliperidone extended-release tablet (paliperidone ER; INVEGA™) is an oral antipsychotic for the treatment of schizophrenia. The recommended dose range is 3–12 mg per day. Paliperidone ER utilizes the OROS® delivery system, which allows for once-daily dosing. Its pharmacokinetic profile results in a more stable serum concentration. Paliperidone is 9-hydroxyrisperidone, the chief active metabolite of risperidone. It undergoes limited hepatic metabolism, thereby minimizing the risks of hepatic drug–drug and drug–disease interactions. Three 6-week trials in patients with acute schizophrenia reported that paliperidone ER was effective, well tolerated, and produced clinically meaningful improvements in personal and social functioning compared with placebo. Post-hoc analysis of these trials in various populations, including recently diagnosed, elderly and more severely ill patients, those with sleep disturbances and those with predominant negative symptoms demonstrated improvement as well. Paliperidone ER was also significantly better than placebo in the prevention of symptom recurrence in a 6-month maintenance study. The most common clinically relevant adverse events associated with paliperidone ER were extrapyramidal symptoms, tachycardia and somnolence. The incidence of Parkinsonism, akathisia and use of anticholinergic medications increased in a dose-related manner. Further, modest QTc interval prolongation was observed but did not produce clinical symptoms. Similar to risperidone, paliperidone ER is associated with increases in serum prolactin levels. Overall, paliperidone ER was effective, well tolerated and provides a new treatment option for patients with schizophrenia.

Keywords: paliperidone, extended-release, antipsychotic, schizophrenia

Introduction

Schizophrenia is a chronic disorder that affects about 1% of the world's population. While presently available antipsychotics can ameliorate an acute exacerbation of positive symptoms (eg, hallucinations and delusions), their benefit for deficit, cognitive and mood symptoms are not as pronounced. Furthermore, the safety and tolerability of each agent may differ substantially, often determining the clinician's initial choice of drug and patients' willingness to adhere to treatment (Janicak et al 2006). Paliperidone extended-release tablet (paliperidone ER) (INVEGA™, Johnson & Johnson Pharmaceuticals, Titusville, NJ, USA), the 9-OH metabolite of risperidone, has recently received approval by the United States (US) Food and Drug Administration (FDA) and by the European Medicines Evaluation Agency (EMEA). This agent combines the efficacy of risperidone with an innovative, osmotically-controlled oral delivery system called OROS™, which releases the drug at a controlled rate specific to the properties of 9-OH risperidone (Conley et al 2006). This allows for once-daily dosing and can minimize the 24-hour peak-to-trough variation at steady state concentration (C_{ss}). Furthermore, its limited hepatic metabolism may reduce drug–drug or drug–disease interactions and its novel delivery system allows for a drug-specific controlled release that produces a more sustained, even exposure over time. While 9-OH risperidone has been identified as an important component of risperidone's effects, it has not been studied previously as an antipsychotic for schizophrenia.

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The purpose of this article is to review the pharmacodynamic, pharmacokinetic, efficacy and safety/tolerability profile of paliperidone ER, the major active metabolite of risperidone.

Methods

The background data to provide this review were derived from a search of PUBMED, EMBASE, and several international congresses (between January 2004 and May 2007) using the key word "paliperidone". It should be noted that many of the studies discussed are presently available only in abstract form and have not been peer reviewed. The three acute pivotal studies and recurrence study, however, have all been accepted or published in peer-reviewed journals.

Results

OROS formulation

Paliperidone ER is formulated within an osmotically controlled release oral delivery system called OROS. The OROS formulation delivers paliperidone at a controlled rate over a 24-hour period. The system consists of an osmotically active trilayer core surrounded by a semi-permeable membrane. The trilayer core contains two drug layers and a push compartment (Figure 1). After administration, water passes through the semi-permeable membrane, thereby controlling the rate of passage into the tablet membrane core, which in turn, controls drug delivery (Conley et al 2006). The OROS technology results in reduced fluctuations between drug peak and trough serum concentrations (eg, 38% paliperidone ER versus 125% risperidone immediate-release [IR]) (Rossenu et al 2007). To preserve the integrity of the OROS delivery system, the tablet should be swallowed whole and not chewed, split or crushed (INVEGA package insert 2007). Since the shell of the tablet is non-absorbable, prescribers should inform patients that the undissolved residue may be observed in their stool.

Pharmacodynamics/pharmacokinetics of paliperidone ER

Pharmacodynamics

Paliperidone is a benzisoxazole derivative that demonstrates high affinity for central dopamine$_2$ and serotonin$_{2A}$ receptors. In addition, it has affinity for both alpha-adrenergic$_{1 \text{ and } 2}$ and histaminic$_1$ receptors. Paliperidone does not possess affinity for muscarinic-cholinergic and beta-adrenergic

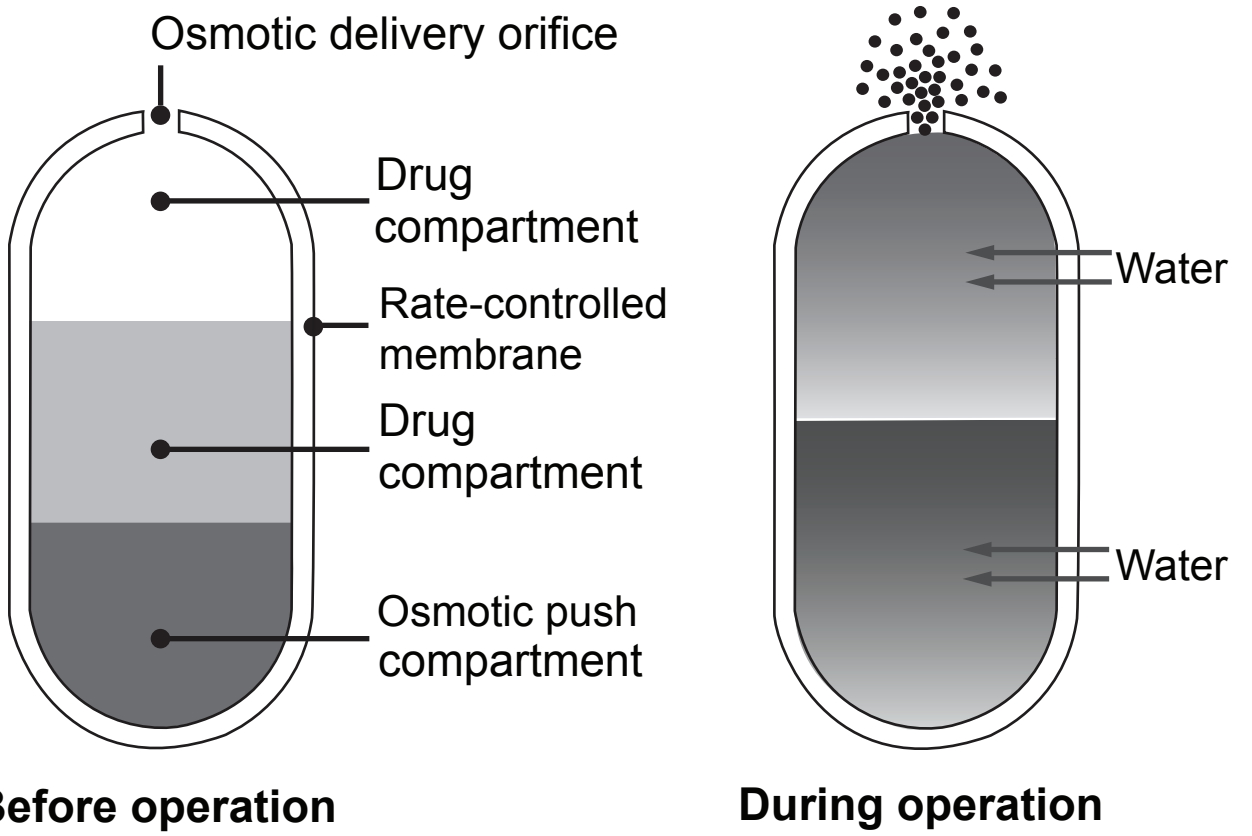

Figure 1 OROS delivery system. The osmotic push–pull tablet: cross-section of bilayer tablet before and after ingestion. Reprinted with permission from Conley R, Gupta SK, Sathyan G. 2006. Clinical spectrum of the osmotic-controlled release oral delivery system (OROS®), an advanced oral delivery form. *Curr Med Res Opin,* 22:1879–92. Copyright © 2006 Informa Healthcare.

receptors. In vitro, the enantiomers (+ and –) of paliperidone demonstrate similar pharmacologic activity.

Pharmacokinetics

The absolute oral bioavailability of paliperidone ER is 28% (INVEGA package insert 2007). Administration of this agent after a high-fat or high-calorie meal increased the maximum serum concentration and area under the curve values by 60% and 54%, respectively. While paliperidone ER can be taken without regard to meals, the presence of food may increase its exposure (INVEGA package insert 2007). Patients in the clinical efficacy trials, however, were dosed without regard to meal timing. The terminal half-life of paliperidone ER is about 23 hours with steady state concentration attained in 4–5 days (Rossenu et al 2006; INVEGA package insert 2007).

Paliperidone ER is widely and rapidly distributed after oral administration. It is 74% protein bound, primarily to albumin and α1-acid glycoprotein. Paliperidone ER undergoes very limited hepatic metabolism, with approximately 60% of the unchanged drug eliminated renally and 11% eliminated unchanged in the feces (Vermeir et al 2005). Paliperidone ER does not appear to possess enzyme-inducing or enzyme-inhibiting properties as shown by the lack of CYP 450 inhibition in in vitro studies in human liver microsome studies (INVEGA package insert 2007). Thus, it is less prone to hepatic drug–drug or drug–disease interactions. While paliperidone ER undergoes both active and passive renal elimination, its co-administration with trimethoprim, a potent organic cation inhibitor, did not significantly alter its clearance rates (Thyssen et al 2006a). Overall, the paliperidone ER pharmacokinetic profile demonstrates dose proportionality within the recommended clinical range of 3–12 mg/day (Rossenu et al 2006).

Hepatic impairment

There may be a higher incidence of liver problems (eg, alcohol-related; hepatitis C) in patients with schizophrenia compared with the general population (Carney et al 2006). In this context, the pharmacokinetic parameters of paliperidone ER were also assessed in patients with moderate hepatic impairment compared with healthy controls (Thyssen et al 2006b). There were minimal differences in the terminal elimination half-life between these two groups (26.5 hours for hepatically impaired patients versus 23.6 hours for healthy subjects). In addition, there was a small reduction in the total exposure to paliperidone ER in the hepatically impaired patients. After correcting for reduced α1-acid glycoprotein binding secondary to hepatic impairment, however, the total exposure to paliperidone ER was similar between groups. The unbound paliperidone ER levels were slightly lower in the hepatically impaired group as compared with healthy controls. As the unbound drug is most relevant to safety and efficacy, no dosage adjustment is recommended in these patients.

Renal impairment

The dose of paliperidone ER should be lowered in patients with moderate-to-severe renal impairment, since the elimination of paliperidone decreases with decreasing estimated creatinine clearance (INVEGA package insert 2007; Thyssen et al 2007). The exact dose of paliperidone ER should be individualized according to the patient's renal function status. For patients with mild renal impairment (with a creatinine clearance of $\geq$50 to $<$80 mL/min), the maximum recommended dose is 6 mg paliperidone ER once daily. For patients with moderate-to-severe renal impairment (with a creatinine clearance of 10 to $<$50 mL/min), the maximum recommended dose is 3 mg paliperidone ER once daily.

Efficacy in acute trials

The acute efficacy of paliperidone ER has been examined in three studies (Davidson et al 2007; Kane et al 2007; Marder et al 2007). These studies involved a 6-week (at least 14 days as an inpatient), double-blind, randomized, fixed-dose, placebo- and active-controlled (olanzapine 10 mg per day), parallel-group design. The primary outcome measure in all studies was the mean change in total Positive and Negative Syndrome Scale (PANSS) score. Secondary outcome measures included the Marder PANSS factor scores (Marder et al 1997), response rates, Clinical Global Impressions–Severity (CGI-S) scores (Guy 1976) and Personal and Social Performance (PSP) scale scores (Morosini et al 2000; Patrick et al 2006). This last scale allows clinicians to rate personal and social functioning on a 100-point scale in 10-point increments (eg, 1–10 representing lack of autonomy in basic functioning; 91–100 representing excellent functioning). The scale considers four domains of behavior: socially useful activities, relationships, self-care, and disturbing and aggressive behaviors. Improvement by one category (ie, 10 points) reflects a clinically meaningful change.

Marder et al conducted the first study at 74 US centers (Marder et al 2007). It included patients with chronic schizophrenia who were experiencing an acute exacerbation (ie, PANSS score range = 70–120; mean ± standard deviation [SD] baseline score = 94 ± 12) of their disorder. Four hundred and forty-four subjects were randomized and 192 (43%) completed

Table 1 Patient demographics and baseline characteristics in the intent-to-treat population

	Placebo (n = 105)	Paliperidone ER 6 mg (n = 111)	Paliperidone ER 12 mg (n = 111)	Olanzapine 10 mg (n = 105)	Total (n = 432)
Age (years)[a]	42.3 (10.7)	42.1 (10.2)	41.4 (10.7)	40.5 (11.0)	41.6 (10.7)
Sex (%)					
Male	78	68	69	80	74
Female	22	32	31	20	26
Race (%)					
White	48	41	41	42	43
Black	50	58	59	53	55
Asian	0	0	0	4	1
Other	2	1	1	1	1
Weight (kg)[a]	89.7 (20.3)	87.4 (19.4)	87.0 (21.6)	89.7 (23.2)	88.4 (21.1)
PANSS total score[a]	93.6 (11.7)	92.3 (12.0)	94.1 (11.4)	94.9 (12.4)	93.7 (11.9)

[a]Mean (standard deviation).
Abbreviations: ER, extended release; PANSS, Positive and Negative Syndrome Scale.
Adapted with permission from Marder SR, Kramer M, Ford L et al 2007. Efficacy and safety of paliperidone extended-release tablets: results of a 6-week, randomized, placebo-controlled study. *Biol Psychiatry*, June 28; [Epub ahead of print] doi:10.1016/j.biopsych.2007.01.017. Copyright © 2007 Elsevier.

the study. The treatment arms included paliperidone ER (6 or 12 mg fixed doses), placebo, and olanzapine (10 mg). Since the olanzapine arm was an active control group to confirm assay sensitivity, it was not included in the statistical models for efficacy analyses. The demographic and baseline characteristics of the 432 intent-to-treat (ITT) patients (ie, randomized patients who received ≥1 dose of double-blind study drug and had ≥1 post-baseline efficacy measure) were similar across all groups (see Table 1). Rescue medications (primarily lorazepam) were used by approximately 75% of subjects in each group for a mean duration of approximately 8 days. The primary outcome measure was change in the PANSS total score from baseline to end point. Both doses of paliperidone ER separated to a statistically significant degree in comparison with placebo (6 mg dose, $p = 0.006$; 12 mg dose, $p < 0.001$). There was also a significant difference from placebo at every post-baseline rating from Day 4 onward in the 6 mg dose group ($p < 0.05$), and from Day 15 onward in the 12 mg dose group ($p < 0.05$). Clinical response rates (defined by ≥30% improvement from the baseline PANSS total score) were also significantly higher in the paliperidone groups versus the placebo group (6 mg = 50% [$p < 0.03$]; 12 mg = 51% [$p = 0.012$]; placebo = 34%). By comparison, the response rate in the olanzapine (10 mg) group was approximately 46%.

Substantially fewer subjects on paliperidone ER were classified as "marked/severe/extremely severe" on the CGI-S scale at end point compared with baseline (6 mg = 57.6% to 26.1%; 12 mg = 64.0% to 20.7%; placebo = 60.0% to 44.7%). By comparison, the olanzapine (10 mg) group went from 70.5% to 29.6%. While PSP scale scores improved in both paliperidone ER dose groups, only the 6 mg dose separated from placebo to a statistically significant degree ($p = 0.007$).

The second trial by Kane et al was similar to the Marder study but had some important design differences. These included the involvement of sites in both the US and India and three fixed doses of paliperidone ER (6, 9, and 12 mg). Six hundred and thirty patients entered and 415 (66%) completed the study (Kane et al 2007). Demographic and baseline characteristics, as well as use and duration of rescue medications (mainly lorazepam), were similar across the four treatment arms. All three doses of paliperidone ER separated to a statistically significant degree from placebo based on the mean change in the PANSS total ($p < 0.001$) and all five Marder factor scores from baseline to end point ($p < 0.001$). Mean PANSS total change scores with paliperidone ER were significantly greater than placebo for the 12 mg dose from Day 4 onward ($p < 0.01$), and for the 6 mg and 9 mg doses from Day 8 onward ($p < 0.05$) (Figure 2). Response rates were almost double in the paliperidone ER groups (6 mg = 56%; 9 mg = 51%; 12 mg = 61%) versus placebo (30%; $p < 0.001$). By comparison, the response rate in the olanzapine (10 mg) group was 52%.

Rates of discontinuation due to lack of efficacy were also lower in the paliperidone ER versus placebo group (6 mg = 16%; 9 mg = 16%; 12 mg = 10%; placebo = 40%). A substantially lower percentage of subjects were classified as "marked/severe/extremely severe" on the CGI-S score from baseline to end point (paliperidone: 6 mg = 63% to 21%; 9 mg = 57% to 23%; 12 mg = 64% to 16%) compared with placebo (60% to 51%). By comparison, the olanzapine (10 mg) group went from

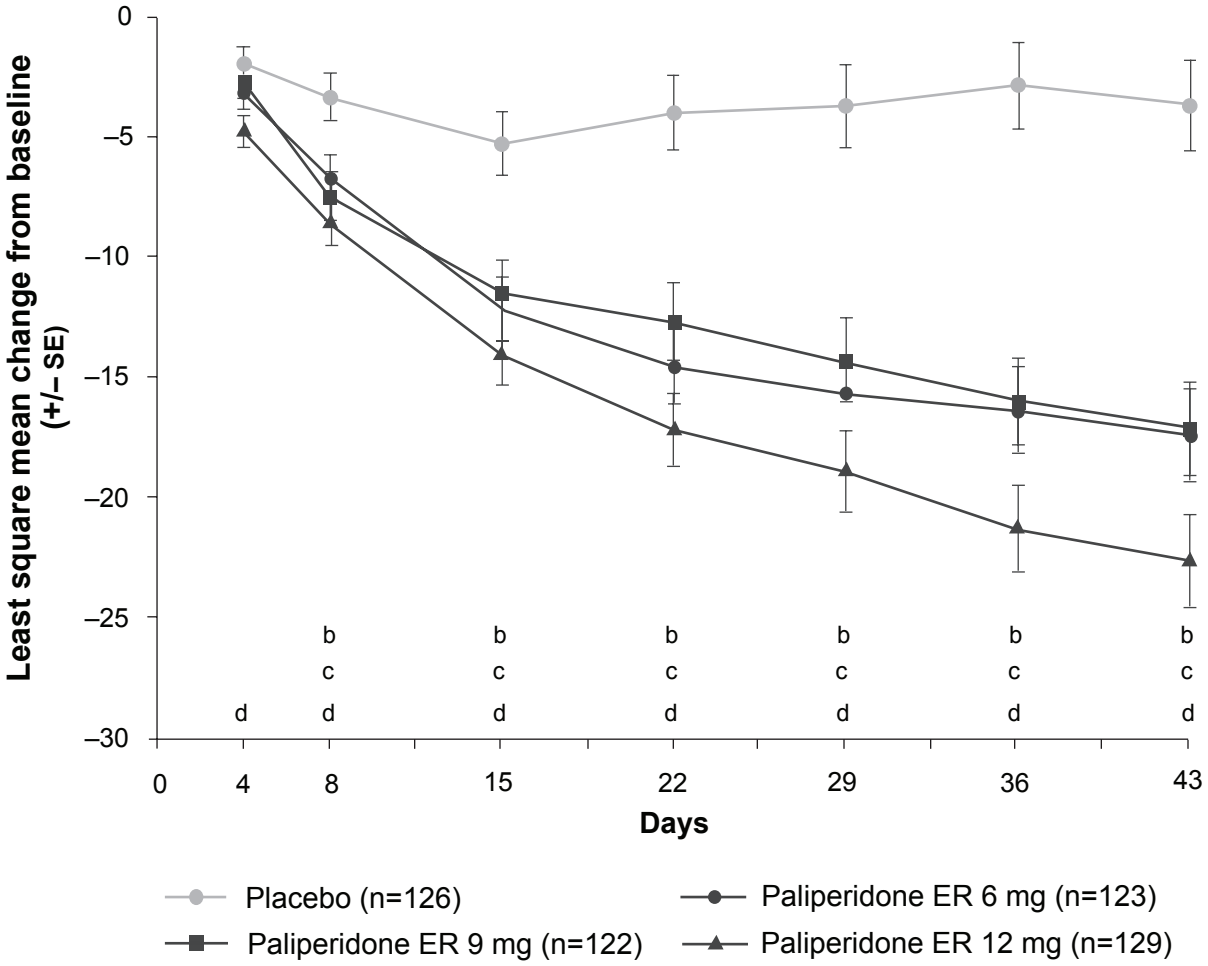

Figure 2 Change in positive and negative symptom scale total score over time in the intent-to-treat population[a] (Kane et al. 2007). Improvement in mean PANSS total score for paliperidone ER versus placebo was statistically significant at every post-baseline time point from Day 4 (first observation point) for paliperidone ER 12 mg ($p < 0.01$ versus change in placebo group), and from Day 8 for the paliperidone ER 6 and 9 mg groups ($p < 0.05$ versus change in placebo group). This was maintained for the remainder of the study in both groups. [a]Last-observation carried forward; [b]Paliperidone ER 6 mg, $p < 0.05$; [c]Paliperidone ER 9 mg, $p < 0.05$; [d]Paliperidone ER 12 mg, $p < 0.01$.
Abbreviations: ER, extended-release; SE, standard error.
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64% at baseline to 24% at end point. Finally, PSP scale scores improved significantly from baseline to end point for all three doses of paliperidone ER compared with placebo ($p < 0.001$) (Figure 3).

The third study by Davidson et al was also similar to the Marder and Kane studies with the following important differences. This was a multi-center, international trial that included three fixed doses of paliperidone ER (3 mg, 9 mg, and 15 mg). Six hundred and eighteen patients were randomized and 365 (59%) completed the study (Davidson et al 2007). As in the Marder et al and Kane et al trials, demographic and baseline characteristics, as well as the use and duration of rescue medications, were similar across all groups.

All paliperidone ER doses produced significantly greater improvements in the PANSS total and Marder factor scores at end point versus placebo ($p < 0.01$). All three doses demonstrated statistically significant improvement from placebo by Day 4 onward. More than twice as many patients in all three paliperidone ER groups achieved a clinical response at end point versus placebo (3 mg = 40%; 9 mg = 46%; 15 mg = 53%; placebo = 18%; $p \leq 0.005$). By comparison, the proportion of responders in the olanzapine (10 mg) active control group at end point was 52%. Rates of discontinuation due to lack of efficacy were lower in the paliperidone ER groups compared with placebo and decreased in a dose-related manner (ie, 3 mg = 24%; 9 mg = 18%; 15 mg = 12%; placebo = 44%). By comparison, the olanzapine (10 mg) active control group had a 13% discontinuation rate due to inefficacy.

A significant improvement in the mean PSP scale scores (± SD) from baseline to end point was also seen for all three doses of paliperidone ER versus placebo (3 mg = 8.3 ± 17.1;

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