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passing through a laser-drilled hole in the tablet at a predetermined controlled rate. When most of the drug has been released from the first compartment, the second compartment begins to release the drug at a different rate. The two drug layers allow for control over the pattern of release of medication. Paliperidone is then delivered regardless of the patient’s gastric pH or gut motility or the presence of food, depending on the area of the gastrointestinal tract into which the drug is released.9

MECHANISM OF ACTION

It has been proposed that paliperidone effectively treats schizophrenia symptoms by acting as an antagonist on central dopamine type 2 (D2) and serotonin type-2 (5-HT2A) receptors. Other effects are thought to occur by antagonism of the alpha-adrenergic receptors (α₁ and α₂) and histaminergic receptors (H₁). Paliperidone has no cholinergic, muscarinic, or beta-adrenergic activity.7

PHARMACOKINETICS

Metabolism and Elimination

The cytochrome P450 (CYP 450) isoenzyme system does not play a significant role in the metabolism of paliperidone. The metabolic pathways identified account for less than 10% each of the drug’s metabolism, including dealkylation, hydroxylation, dehydrogenation, and benzisoxazole scission (fission).7 The limited metabolism of paliperidone suggests no expectation of important metabolic interactions.

No differences are noted between patients who are extensive metabolizers and those who are poor metabolizers of CYP 2D6 substrates, as is the case with risperidone, the parent molecule.7,10

Absorption

After oral administration, the absolute bioavailability of paliperidone is 28%. The manufacturer states that paliperidone can be taken without regard to meals. However, the presence of food, especially high-fat or high-calorie meals, increases the bioavailability of the drug up to 60%, compared with fasting states.7

INDICATIONS

Paliperidone was approved in December 2006 for the acute treatment of schizophrenia and for the long-term maintenance treatment of schizophrenia in April 2007.11

CLINICAL EFFICACY

Kane et al.12 Kane and colleagues conducted a six-week, double-blind, placebo-controlled, active-controlled, fixed-dose study of extended-release (ER) paliperidone in strengths of 6, 9, and 12 mg. The study included 630 patients. To be enrolled, patients had to:

- be older than 18 years of age
- be experiencing an acute episode of schizophrenia at time of screening
- have a diagnosis of schizophrenia for at least one year prior to screening
- be willing to be voluntarily hospitalized for a minimum of 14 days

Patients were excluded from the trial if they:

- had a diagnosis of substance dependence
- had a medical condition that could affect the absorption, metabolism, or excretion of paliperidone
- were at significant risk for suicide or violent behavior
- were receiving other medications or not receiving a stable dose for at least three months (antidepressants, mood stabilizers, and benzodiazepines).

Patients who met the inclusion and exclusion criteria were randomly assigned to receive paliperidone ER 6 mg, 9 mg, or 12 mg; placebo; or olanzapine 10 mg (Zyprexa, Eli Lilly) once daily in the morning for six weeks. No dose titration or dose changes were allowed during the study. All previous medications that were not administered as a stable dose for the previous three months were discontinued for three days before randomization. Patients were hospitalized at the start of randomization for a minimum of 14 days and were then monitored weekly until the end of the six-week trial.

Primary outcome measures were scores from the Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impressions–Severity (CGI–S) Scale. Baseline demographics were similar for all treatment groups. The most common diagnosis was paranoid schizophrenia. The mean baseline PANSS score was 93.9 ± 11.0, which indicates severe schizophrenic symptoms.

Of the 630 patients enrolled, 66% completed the six-week study. There were more dropouts in the placebo group (54%) than in the other groups (22–35%), whereas the patients receiving paliperidone ER 12 mg had fewer dropouts than any other group (22%).

Discontinuation of treatment resulting from adverse drug events (ADEs) was low and similar for all treatment groups (3%–7%). The most common ADE that led to discontinuation was tachycardia (2% in patients receiving paliperidone ER 12 mg and 1% in all other groups).

The most frequently reported ADEs in the paliperidone ER groups were tachycardia, EPS, and hyperkinesias. There was a trend toward more EPS with the higher doses. Insomnia was reported at equal rates in all treated patients, including those receiving placebo.

During this six-week trial, there were no statistically significant changes in fasting glucose, insulin, or serum lipid levels. A weight increase of more than 7% was seen in 3% to 7% of the paliperidone ER patients and in 13% of the olanzapine patients. Six patients receiving paliperidone ER experienced prolactin-related ADEs; as a result, two patients discontinued the study. Mean prolactin levels were elevated in patients receiving paliperidone ER.

For all patients receiving treatment, when compared with those receiving placebo, the mean decrease from baseline in PANSS scores was statistically significant. The mean decreases in PANSS scores were −17.9 ± 22.2 with paliperidone ER 6 mg, −17.2 ± 20.2 with 9 mg, and −23.3 ± 20.1 with 12 mg.

For the placebo group, the reduction in PANSS scores was −4.1 ± 23.2; for the olanzapine group, it was −19.9 ± 19.0. In addition, 22% of patients receiving 6 mg, 23% receiving 9 mg, and 32% receiving 12 mg experienced a minimum 50% reduction in PANSS scores, compared with 15% of patients receiving placebo.

With the CGI–S scale, 21.3% of patients receiving paliperidone ER 6 mg, 23% receiving 9 mg, and 6.3% receiving 12 mg were classified as “markedly ill” or “severely ill” at six weeks, compared with 50.8% in the placebo group. In the Kane
research, all three doses of paliperidone ER demonstrated statistically significant improvement when compared with placebo; results were comparable to those of olanzapine.

Kramer et al.13

A study by Kramer and associates also evaluated the efficacy of paliperidone ER in a multiphase trial. In an eight-week run-in phase, 530 patients were hospitalized and received open-label paliperidone. Dosing was flexible, starting at 9 mg once daily, and the dose could be adjusted between 3 and 15 mg once daily. The most commonly used dose was 9 mg. The dose was increased to 12 or 15 mg in 47% of patients and was decreased to 3 or 6 mg in 8% of the patients.

A total of 312 of the 530 patients completed the run-in phase and entered the second phase. Of those patients who dropped out, 22 discontinued treatment because of ADEs, 27 were lost to follow-up, and 78 withdrew by their own choice.

After patients were deemed stable for at least two weeks, they entered a six-week, open-label stabilization phase. During this phase, the patients remained on the fixed dose of paliperidone ER that had been established during the run-in phase. In this phase, doses of 9, 12, and 15 mg were used equally in 33%, in 26%, and in 30% of patients, respectively.

After the six-week stabilization phase, 207 patients entered a double-blind phase; 105 were randomly selected to continue receiving paliperidone ER, and 102 were switched to receive placebo. Patients were maintained in the double-blind phase until symptoms recurred, until the patients withdrew from the study, or until the study was completed.

The final results showed an average of 23 days to symptom recurrence with placebo and 83 days with paliperidone ER. Fifty-two placebo patients experienced a recurrence, compared with 23 paliperidone ER patients. On the basis of these data, the FDA granted an indication for paliperidone ER in the maintenance treatment of schizophrenia.

The most commonly reported ADEs included tremor (16%), headache (14%), hyperkinesias (12%), and insomnia (10%). Tachycardia was reported by 15% of patients treated with paliperidone ER. The average weight gain was 1.8 kg with paliperidone ER and 0.2 kg with placebo.

There were no statistically significant changes in laboratory values for glucose, insulin, or lipid levels.

**DOSEAGE**

**Adults**

On the basis of the Kane and Kramer studies,12,13 the recommended initial starting dose of paliperidone is 6 mg/day. This dose is adjusted, as needed, to a maximum of 12 mg/day. Adjustments should be made in 3-mg increments over a five-day period.7

**Special Populations**

**Elderly Patients.** Kane et al. also reviewed paliperidone’s safety and tolerability in 114 patients 65 years of age and older in one six-week, double-blind, placebo-controlled study.14 Patients were randomly selected to receive placebo or doses of paliperidone ranging from 3 to 12 mg. ADEs were comparable with those of placebo except for hypertonia, tremor, and mild tachycardia, which occurred only within the treatment group. The findings indicated that paliperidone was safe and efficacious at all doses in older patients without the need for dosage adjustments. However, for elderly patients with concurrent renal impairment, dosage adjustments may be necessary.7

**Hepatic Impairment.** According to the manufacturer, no dosage adjustments for paliperidone are needed in patients with mild-to-moderate hepatic impairment. Plasma levels of the drug in 10 patients with moderate hepatic impairment (Child-Pugh class B), when compared with 10 healthy subjects, were similar in a single-dose parallel-group, single-center study.15 The use of paliperidone has not been studied in severe hepatic impairment; consequently, no recommendations have been made.7

**Renal Impairment.** Mild renal impairment, characterized by a creatinine clearance (CrCl) from 50 to 79 mL/minute, resulted in a decrease of total clearance by 32%. The maximum recommended dosage of paliperidone for patients with mild renal impairment is 6 mg/day.

Moderate renal impairment (CrCl, 30–49 mL/minute) showed a 64% decrease in clearance. For patients with severe renal impairment (CrCl, below 29 mL/minute), total clearance decreased by 71%. As a result, the maximum dosage recommended in moderate and severe renal impairment is 3 mg/day.7

**DRUG INTERACTIONS**

Paliperidone is an active metabolite of risperidone, and it does not undergo extensive hepatic metabolism. Preclinical studies suggest that drug–drug interactions should not be clinically significant with paliperidone.9

Paliperidone interacts with CYP 2D6 and CYP 3A4 in vitro. The effects of this interaction are unlikely to result in any clinically significant consequence, because in vivo studies have not shown a decrease in elimination through those isoenzymes.

Similar to other antipsychotic medications, paliperidone may show antagonistic effects when used in combination with dopamine agonists or levodopa. Caution should also be exercised with centrally active drugs and alcohol in patients taking paliperidone.7

**COST**

The manufacturer has estimated paliperidone’s average wholesale price (AWP) on a per-day basis. The retail price of the 3-mg and 6-mg formulations is $9.76 for once-daily dosing. The 9-mg once-daily formulation is approximately $14.64. This price may vary among different health care systems.

These price ranges are comparable to those of similar antipsychotic drugs such as risperidone. The estimated AWP of risperidone twice daily on a per-day basis is $7.08 for 1 mg, $11.84 for 2 mg, $13.90 for 3 mg, and $18.66 for 4 mg.

**CONCLUSION**

Paliperidone represents another viable option for treating schizophrenia. Clinical trials have demonstrated its effectiveness for patients with this illness versus placebo in both the acute and the chronic phases. The advantages of paliperidone include once-daily dosing, fewer drug interactions, and less sedation.

**REFERENCES**


