



A review of paliperidone ER: pharmacology and drug–drug interactions

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Paliperidone extended-release (paliperidone ER; Invega™, Janssen) is a new “atypical” antipsychotic compound that has been formulated with the OROS® technology, which is an osmotic controlled release oral delivery system. It allows the product to be administered once a day.

Paliperidone ER is a member of the benzoxiazole family. The compound contains a racemic mixture of (+) and (–) paliperidone; both forms have similar activity.

Pharmacodynamic & Pharmacokinetic Profile

Paliperidone is a known antagonist of dopamine D₂, serotonin 5-HT_{2A}, histamine H₁, and α₁- and α₂-adrenergic receptors; it has no affinity for the cholinergic muscarinic or β₁- and β₂-adrenergic receptors. A single dose of paliperidone ER 6 mg in healthy volunteers (n=4) produced a median D₂ receptor occupancy of 64% at 22 hours and 53% at 46 hours. The estimated effective dose of paliperidone ER (>60% D₂ receptor occupancy) was predicted to be higher than 3 mg. Pivotal studies have now determined the optimal dose to be 6 mg.

Thus, paliperidone ER acts as a D₂, 5HT_{2A} antagonist compound, which is a well known activity profile among second generation antipsychotic compounds developed for the treatment of schizophrenia. As paliperidone does not bind to muscarine receptors, it does not cause the anticholinergic side effects such as dry mouth, diplopia, constipation or dysuria.

D₂ blocking activities are associated with antipsychotic (positive symptoms), extrapyramidal symptoms (EPS) and prolactin secretion. 5HT_{2A} occupancy is associated with antipsychotic activity (negative symptoms) as well as protection against EPS. A review of paliperidone ER indicates that this compound shows high clinical efficacy on both positive and negative symptoms, with less propensity to weight gain and sedation and a remarkable safety profile; especially on EPS.

The pharmacokinetic profile of paliperidone ER has been evaluated in several studies in healthy volunteers. In order to avoid peak-to-trough blood variations in plasma, and to produce steady release of the active drug, paliperidone has been formulated with the OROS® technology. Single doses of paliperidone ER from 3 to 12 mg demonstrated dose-dependent pharmacokinetic properties. In healthy volunteers (n=4) given a single dose of paliperidone ER 6 mg, the mean maximum plasma concentration (C_{max}) was 11.7 ng/mL and the mean time to achieve that maximal concentration

(t_{max}) was 25.1 hours. The mean area under the plasma concentration–time curve (AUC) from time 0 to 48 hours was 302 ng•h/mL.

Paliperidone is administered as a racemic mixture of (+) and (–) enantiomers. Both enantiomers interconvert in humans. 74% of racemic paliperidone is bound to plasma protein. There was a difference between both enantiomers regarding the medial volume of the peripheral compartment: which was 192 L for the (–) and 70.6 L for the (+) enantiomer. At steady state, the AUC for the (+) enantiomer was 1.6 fold greater than for the (–) enantiomer.

Paliperidone ER has a terminal elimination half life (t_{1/2β}) of approximately 23 hours. The period of time to achieve plasma steady-state is 4–5 days. The administration of a single dose of paliperidone ER at a dose of 9 mg showed that the mean steady-state peak-to-trough ratio was 1.7 (range 1.2–3.1), which is a very steady release profile as compared with other oral atypicals and even with long acting formulations.

Minimal Liver Metabolism

Paliperidone ER is a major metabolite of risperidone and studies performed in humans showed that paliperidone ER is mainly eliminated, unchanged, through the renal route (Table). That is why the pharmacokinetic profiles after paliperidone administration were similar in poor and extensive metabolisers of CYP2D6 determined by dextromethorphan-O-demethylation phenotype. In healthy volunteers administered with 1 mg ¹⁴C paliperidone, 91% of the radioactivity was recovered, 79.6% in the urine and 11.4% in the faeces. In the urine, most of the dose (mean 59.4%) was excreted unchanged; the remainder was eliminated as metabolites by de-alkylation (4.6%), hydroxylation (3.8%), dehydrogenation (2.7%) and benzisoxazole scission (4.1%) pathways. In faeces, two metabolites were identified; each accounted for <1% of the administered dose.

Lack of Drug–Drug Interactions

Schizophrenia patients are highly prone to polypharmacy. In the case of paliperidone, there are no significant drug–drug interactions. The reason is that this new second generation “atypical” antipsychotic does not undergo significant metabolism and is mainly excreted unchanged. Therefore, systemic exposure to paliperidone is not altered with concomitant administration of drugs with P-glycoprotein or CYP3A4-inducing or -inhibiting

Table. Comparison of the metabolism and dosage of atypical, second-generation antipsychotics.

Drug	Dosage (oral)	CYP metabolism and other metabolic pathways	Excretion	Dosage modification in renal/liver disease
Clozapine	1 st day: 12.5 mg once daily-bid 2 nd day: 25–50 mg/day Titrated up to 300–450 mg/day in divided doses within 14–21 days Max 900 mg/day	CYP1A2, CYP3A4 Minor CYP2D6	50% in urine 30% in faeces	Avoid in patients with severe renal impairment or liver disease Use with caution in patients with mild-moderate renal impairment
Risperidone	Initial 2 mg/day bid or qid Titrated up to 4–6 mg/day	CYP2D6, CYP3A4	70% in urine 14% in faeces	Reduce starting dose to 0.5 mg bid in renal and liver disease
Olanzapine	Initial 10 mg once daily Titrated up to 15 mg/day	CYP1A2, Minor CYP2D6 N-glucuronidation	57% in urine	Reduce starting dose (50%) in renal and liver disease
Quetiapine	Initial 25 mg bid Titrated up to 200–800 mg/day	CYP3A4 Minor CYP2D6	75% in urine 21% in faeces	Reduce starting dose (50%) in renal and liver disease
Ziprasidone	Initial 40 mg bid Titrated up to 80 mg bid	Minor CYP3A4, CYP1A2 Aldehyde oxidase	20% in urine 66% in faeces	Use with caution and/or lower doses in patients with hepatic impairment
Aripiprazole	10–30 mg/day	CYP2D6, CYP3A4	25% in urine 55% in faeces	No dosage adjustment
Paliperidone	6 mg once daily is suitable for most patients	None	80% in urine 11% in faeces	3 mg starting dose for moderate to severe renal impairment

properties, CYP2D6-inhibiting properties, nor with drugs having effects on gastrointestinal motility, stomach pH and rate of gastric emptying, or with diuretics, laxatives and anticholinergics.

Paliperidone ER did not substantially inhibit the metabolism (and therefore clearance) of drugs metabolized by the cytochrome P450 isoenzymes, including CYP1A2, CYP2A6, CYP2C8/10, CYP2D6, CYP2E1, CYP3A4, and CYP3A5 in an in vitro study in human liver microsomes.

This lack of interaction of paliperidone ER with the cytochrome P450 metabolic pathway was evaluated in the analysis of the pooled clinical data of 616 schizophrenic patients treated with paliperidone ER, looking at CYP2D6 poor metabolizers and their incidence of potential side effects. The conclusion of this study was that in these clinical trials, it was impossible to detect a higher incidence of adverse events in patients receiving paliperidone ER with a CYP2D6 poor metabolizer phenotype as compared with patients with a normal CYP2D6 metabolizer phenotype. In conclusion, drug interactions between paliperidone and drugs metabolized through cytochrome P450 enzymes are considered unlikely in a clinical setting.

Another study assessed the effect of trimethoprim (TRI), a potent inhibitor of organic cation transport, on the pharmacokinetics of orally administered paliperidone ER. In 30 healthy male subjects TRI administered at 200 mg twice daily for 5 days had no significant effect on the pharmacokinetic parameters (C_{max} , t_{max} , AUC, renal clearance and amount of drug excreted unchanged in the urine) with a single dose of 6 mg paliperidone ER.

Paroxetine, a commonly used antidepressant, is a potent CYP2D6 inhibitor; therefore a pharmacokinetic drug–drug interaction was performed on paroxetine against a single dose of 3 mg paliperidone ER. Paroxetine 20 mg daily given for 13 days was associated with a slight increase in systemic exposure to paliperidone given on day 10, with ratios of 1.16 (CI 1.04–1.30) for AUC and 1.09 (CI 0.98–1.22) for C_{max} which were not

considered clinically relevant. There were no statistically significant differences in clinical or laboratory adverse events between the doses of paliperidone ER given with or without paroxetine.

Special Patient Populations

In patients with mild renal impairment with creatinine clearance (CL_{cr}) 50–80 mL/min [3.0–4.8 L/h], the terminal elimination half-life ($t_{1/2\beta}$) was 24 hours compared to a $t_{1/2\beta}$ of 23 hours in controls with normal renal function. With moderate renal impairment (CL_{cr} 30 to <50 mL/min [1.8 to <3.0 L/h]), the $t_{1/2\beta}$ was 40 hours and with severe renal insufficiency (CL_{cr} 10 to <30 mL/min [0.6–1.8 L/h]), the $t_{1/2\beta}$ was 51 hours.

The total clearance of paliperidone decreased with decreasing CL_{cr} values by 32% with mild, 64% with moderate and 71% with severe renal impairment, corresponding to a mean increase in systemic exposure to the active drug, as assessed by AUC from time 0 to infinity of 1.5, 2.6 and 4.8-fold that of healthy volunteers, respectively. Age, gender, race or mild to moderate hepatic impairment did not affect the pharmacokinetics of paliperidone ER.

Conclusions

Paliperidone ER is a once daily antipsychotic, which provides 24 hr control and constant drug levels, improving safety, reducing dosing frequency and providing a uniform drug action. An effective starting dose can be used without the need for dose titration. Paliperidone shows limited metabolism. This compound is excreted almost entirely unchanged with minimal participation of CYP450 enzymes. Patients who are CYP2D6 poor metabolizers did not show increased incidence of serious adverse events as compared to CYP2D6 extensive metabolizers. Studies performed on drug–drug interactions showed no major pharmacokinetic interactions. The general consensus is that paliperidone ER has a low risk of drug–drug interaction.