

Paliperidone: A Clinical Review

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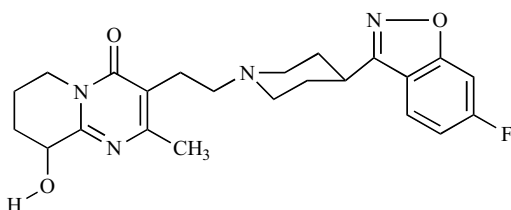
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Abstract: Paliperidone is an antipsychotic recently made available in the US and UK in a special oral extended release form. Paliperidone is a modified form of risperidone namely 9-hydroxyrisperidone, (itself the active metabolite of risperidone). Since risperidone has been available for many years some argue that paliperidone is not a novel antipsychotic but a newly marketed variant. An injectable form, paliperidone palmitate is being trialled. Paliperidone is mainly excreted renally and there is only limited hepatic metabolism. Paliperidone works by partially blocking D2 dopamine receptors and fully blocking serotonin. The normal dosing range for paliperidone is 3-12 mg daily. Efficacy studies with paliperidone indicate that it is effective against schizophrenia and also has a similar side effect profile compared to other antipsychotics. There is an absence of effects on glucose and lipids in comparison with olanzapine. Symptom reduction in schizophrenia occurs as soon as day four of treatment with paliperidone. Clinical experience with risperidone over many years suggests that paliperidone would have a valuable role as an antipsychotic. The entity is not truly novel, but rather than being a variant existing purely for marketing purposes, should be regarded as an upgrade.

INTRODUCTION

Paliperidone is a novel antipsychotic researched and manufactured by Janssen, who are also the manufacturers of risperidone. Paliperidone is available in the US and UK as Invega™. Paliperidone is available in an oral form, which is delivered by using the osmotic-release oral system OROS – an extended release system designed to release paliperidone steadily into the bloodstream over a 24-hour period. This form is referred to below as paliperidone ER. A phase III clinical trial is underway for a long-acting injectable formulation of paliperidone palmitate in patients with schizophrenia. The FDA approved paliperidone (Invega™) for the treatment of schizophrenia in 2006.

This review comprises all available papers on paliperidone. The literature is small. The review also focuses on clinically relevant papers on 9-hydroxyrisperidone. There is a literature on 9-hydroxyrisperidone that predates paliperidone. The papers were identified *via* searches of MEDLINE and PsycINFO databases using the search terms paliperidone and 9-hydroxyrisperidone.



The chemical formula for paliperidone is C₂₃H₂₇FN₄O₃ and its systematic name is 3-[2-[4-(6-fluorobenzofuro[2,3-b]isoxazol-3-yl)-1-piperidyl]ethyl]-7-hydroxy-4-methyl-1,5-diazabicyclo[4.4.0]deca-3,5-dien-2-one. Paliperidone is otherwise 9-hydroxyrisperidone, the active metabolite of risperidone. Paliperidone is a racemic mixture (+and – enantiomers) [1].

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PHARMACOLOGY

Paliperidone ER is the active metabolite of risperidone and works by partially blocking D2 dopamine receptors and fully blocking serotonin (5-HT₂) receptors [2] (with high affinity for 5-HT₇ receptors). The OROS drug delivery system is designed to try and keep the D₂ receptor occupancy at a level below 80%, which it is conjectured may minimise adverse effects such as extrapyramidal symptoms [3]. The paliperidone ER formulation at 6 mg daily technically achieves receptor occupancy of above 60%, but below 80% [2].

PHARMACOKINETICS AND METABOLISM

Paliperidone is mainly excreted renally. There is only limited hepatic metabolism. Both cytochrome P450 (CYP) 2D6 and 3A are responsible [4].

The drug delivery system used for paliperidone, called OROS has been used to deliver various other drugs including verapamil and nifedipine. The tablet has an outer coat with two laser-drilled holes. The drug is eventually pushed through these. Initially a water-dispersible colour overcoat is quickly eroded in the GI tract, and then water is absorbed across a semi-permeable membrane into the core. There are two inner drug layers which absorb the water and form a gel incorporating the paliperidone. Finally a third 'push' compartment, absorbs water by osmosis to gradually push the gel drug suspension through the laser drilled holes in the outer coat. The system is vaunted to have an enhanced safety profile, and produce stable drug concentrations avoiding any large peak-to-trough fluctuations in paliperidone concentrations, and permit less frequent dosing [2,5]. Similar antipsychotics – such as olanzapine and risperidone have once daily dosing though and in any case critics of the use of an OROS system may point out that with the drug paliperidone having a relatively long half life a stable steady state should be reached within 4-5 doses without the involvement of a complicated drug delivery system.

A long acting formulation, paliperidone palmitate, has been phase III trialled [6]. The novel formulation relies on

nanocrystal technology to bring the particle size under 200 nm, thus improving solubility.

DOSING

The normal dosing range for paliperidone is 3-12mg daily, dependent upon response [7]. Lower doses reduce the risk of extrapyramidal side effects. The bioavailability of paliperidone after oral administration is 28%. Administration of paliperidone ER with food can increase this bioavailability considerably. A mean dose of about 8mg daily has been found effective in elderly patients [7].

The depot formulation, paliperidone palmitate has been trialled in three doses – 50mg, 100 and 150mg given to patients with schizophrenia once every four weeks over a 14-52 week study period – variant studies having different lengths and presumably differing aims as the shortest study periods would only allow at most four depot doses to be given during the length of the study [6].

CLINICAL EFFICACY

A study by Kramer *et al.* gave a tantalising glimpse of symptom reduction in schizophrenia occurring as soon as day four of treatment with paliperidone [7].

Kramer *et al.*'s (2007) study had various phases including an eight-week run-in phase where 530 hospital inpatients (aged 18-65) with DSM-IV schizophrenia started on 3-15mg of paliperidone until they were judged to be stable [8]. There then followed a further phase for 312 discharged patients where they remained on their previous paliperidone dose over six weeks (referred to as a stabilisation phase) and then a double blind phase during which the patients still in the study (after attrition) received either placebo (n=102) or paliperidone ER (n=105). The primary efficacy measure was then the time to a recurrence of symptoms during the latter double blind phase. The recurrence was judged according to adverse PANSS or CGI scores, psychiatric hospitalisation or suicidal, homicidal or aggressive behaviour. The study was halted early because the interim analysis yielded significant efficacy results. The interim analysis was triggered when there had been 43 recurrence events. More than twice as many recurrences were seen in the placebo treatment group. Time to recurrence was also significantly longer in the paliperidone group.

Kane *et al.* (2007) studied the efficacy and safety of paliperidone ER (in doses of 6 mg, 9 mg and 12 mg daily) versus placebo in 628 patients with acute schizophrenia [9]. The total Positive and Negative Syndrome Scale (PANSS) scores were between 70 and 120. The study was conducted over 53 centres. The study lasted only 6 weeks, but was both double blind and randomised. Exclusion criteria included substance dependence, medical conditions and a history of tardive dyskinesia or neuroleptic malignant syndrome (NMS), pregnancy or breastfeeding, and recent intramuscular depot antipsychotic injections.

In Kane's study all doses of paliperidone ER (6, 9 or 12mg) were associated with a significant improvement in PANSS scores and also ratings of personal and social functioning [9]. The mean decrease in the PANSS score (+/- SD)

across the three doses was between -17.2 (+/- 22.2) and -23.3 (+/- 20.1). Improvement in PANSS scores for the 12mg dose of paliperidone ER versus placebo was significant at every measurement point from day four onwards. Lower doses of paliperidone produced significant effects from day 8. The olanzapine group saw a mean PANSS reduction of -19.9 (+/- 19.0). The 12mg dose of paliperidone saw only 10% of patients being withdrawn due to lack of efficacy compared to 15% in olanzapine (10mg).

There were significant improvements in personal and social functioning across all paliperidone dosages as measured by the (PSP) scale. The PSP scale was devised by Morosini *et al.* and involves a clinician rating of personal and social functioning on a 100-point scale with scores between 1 and 10 representing almost complete lack of autonomy and 91-100 indicating excellent functioning [10].

Davidson *et al.*'s six week multicentre study of 618 randomised patients compared paliperidone with placebo and again found significant improvements on PANSS total scores ($p < 0.001$) with changes from baseline ranging from -15 for 3mg, -16.3 for 9mg to -19.9 for 15mg and personal and social functioning ($p < 0.001$) and echoing other studies noted symptom improvement at day 4 [11].

Clinical efficacy is often difficult to predict at an individual level. Entry of risperidone and 9-hydroxy risperidone into the brain is limited by the glycoprotein transporter [12]. The brain entry of risperidone and 9-OH-risperidone is greatly limited by P-glycoprotein and this glycoprotein is a product of the ATP-binding cassette B1 (ABCB1) gene. ATP binding cassette (ABC) systems are responsible for the import and export of a wide variety of molecules across cell membranes. A recent study by Xing *et al.* (2006) on 130 Chinese patients with schizophrenia found that genetic variation in the ABCB1 gene influenced the individual response to 9-OH risperidone [13]. They concluded that genotyping C1236T may predict efficacy of risperidone treatment as patients with the TT genotype showed greater improvement on the Brief Psychiatric Rating Scale.

In terms of efficacy in the elderly, Tzimos's 2008 double blind placebo controlled study involved 114 patients aged 65 or over with schizophrenia over six weeks, with a six month open label extension [14]. 70% of patients were female and the mean age was 70. Although some improvement was seen in symptom severity efficacy measures did not show consistent statistical improvement in treatment groups.

A reversal of sleep pattern is sometimes seen in schizophrenia. Some research work on the effect of paliperidone on sleep architecture has been done [15]. This placebo-controlled study found that patients reported improved sleep quality without daytime drowsiness and also found objective improvements in sleep architecture. Overall sleep time increase was found and a decrease in mean latency to sleep onset and fewer awakenings after sleep onset.

An *in vitro* study by Zhu *et al.* (2006) suggested that risperidone and paliperidone, may inhibit the uptake of other drugs across the endothelial cells of the blood-brain barrier by their competitive use of the p-glycoprotein transporter

Table 1. Most Common Reported Adverse Effects with Paliperidone – Expressed in Percentages (Kane *et al.*, 2007 [9])

	Placebo (n=126)	Paliperidone 6mg (n=123)	Paliperidone 9mg (n=122)	Paliperidone 12mg (n=130)	Olanzapine 10mg (n=128)
Insomnia	17%	11%	16%	12%	14%
Somnolence	6%	4%	7%	8%	14%
Extrapyramidal disorder	1%	3%	7%	10%	2%
Hyperkinesia (akathisia)	3%	3%	6%	11%	4%
Tachycardia	10%	18%	14%	22%	14%

Prolonged QTc intervals were not found.

system [16]. This study also indicated that risperidone may compete with its own active metabolite, paliperidone, at the glycoprotein level. This raises the possibility that a pure form of paliperidone may avoid this inhibitory competition with risperidone. This interesting concept requires some exploration through *in vivo* study.

In reviewing the efficacy studies it is rather a case of 'so far so good'. What are required are studies running over a longer period and comparing paliperidone directly with both risperidone and alternative atypical antipsychotics.

ADVERSE EFFECTS

An open label study comparing flexibly dosed paliperidone with placebo found comparable adverse event rates between the active drug and placebo: 35% for paliperidone ER and 40% for placebo [8]. The mean weight increase for paliperidone treated patients over the treatment course of 40 weeks was 1.8kg compared with 0.2kg in the placebo group. There were no marked changes in C-peptide, glucose, insulin, or lipid levels in paliperidone treated patients.

Kane *et al.*'s double blind study (2007) involving a larger number of patients found that compared to placebo various doses of paliperidone (9 and 12 mg daily particularly) were associated with elevated movement disorders [9].

In the Kane study paliperidone was not associated with glucose-related adverse effects or clinically relevant changes in plasma lipid levels and changes in mean bodyweight were minimal.

Table 1 indicates the most frequent adverse effects found in the Kane *et al.* study. Predictably the incidence of adverse events increases with the dose of paliperidone. A similar level of adverse events was observed with olanzapine 10mg, which was another of the treatment arms. The incidence of movement disorders was less with olanzapine compared to paliperidone. Mean body weight change was higher with olanzapine, but the study only extended across six weeks. Bodyweight changes with paliperidone appear dose dependent and ranged from 0.2- 0.9 kg across the short Kane study. The weight increase was greater across the 24-week run of the 2007 Kramer study, which found an increase of 1.8kg, compared to 0.2 kg in the placebo group [8].

Prolactin related adverse events were found in about 1% of patients on paliperidone [18]. It was Melkersson (2006) and Knegeting (2005) who established that the prolactin level increase is primarily associated with the concentration of the 9-hydroxy metabolite of risperidone rather than serum levels of risperidone, suggesting that paliperidone may be more potent in elevating prolactin than risperidone [16, 17]. Kramer's 2007 study found prolactin related adverse events in 4% of paliperidone ER patients compared to 0% of the placebo group [8]. Clinically this may prove to be an important point affecting acceptability to female patients and consequent compliance.

Meyer *et al.* conducted an analysis of pooled data of three six week, double blind, placebo controlled studies (n=1306) and found no clinically relevant changes in mean total cholesterol, triglycerides, HDL or LDL, or glucose levels [19].

In the elderly Tzimos *et al.* found that paliperidone had a similar side effect profile to placebo [14]. During the double-blind phase, discontinuation rates due to adverse events were similar between groups (paliperidone: 7%, placebo: 8%) as were incidences of adverse events (paliperidone: 67%, placebo: 71%). Serious adverse events occurred in 3% of the paliperidone and 8% of the placebo-treated patients. Half of the patient had elevated prolactin levels, but no prolactin- or glucose treatment-related adverse events or significant changes in body weight occurred.

CAUTIONS AND CONTRAINDICATIONS

Paliperidone is mainly excreted renally. Significantly lower oral and depot doses would be required in patients with any renal impairment.

9-hydroxyrisperidone is known to transfer from breast-feeding mothers into breast milk, but the short-term risks to infants are thought to be low as the resultant infant serum levels of the drug are minimal [20].

In mild or moderate hepatic impairment there is little need to modify doses of paliperidone [21]. Lower protein binding of paliperidone in hepatically impaired patients means a higher unbound fraction (35%) compared with paliperidone in healthy subjects (28%). Overall though the expo-

sure to paliperidone was similar in both hepatically impaired and healthy subjects.

INTERACTIONS

The fundamental similarity to risperidone in that paliperidone is a metabolite of risperidone would suggest that clinically significant interactions should be no more problematic than for risperidone itself.

Second-generation antipsychotics, on the whole tend to be mainly metabolised by CYP enzymes [22]. If co-prescribed with inducers or inhibitors of CYP enzymes, antipsychotic plasma levels are increased or reduced accordingly. This may naturally lead to reduced effectiveness or increased adverse events. Predictably therefore interactions with carbamazepine and paroxetine could occur.

A dose dependent interaction with higher doses of paroxetine has been noted with risperidone, such that higher serum levels of risperidone and 9-hydroxy risperidone were found when doses of 40mg paroxetine were co administered [23]. This effect may also occur at higher doses of co-administered sertraline (e.g. 150 mg daily) [24]. Whether this effect occurs with paliperidone alone is not clear.

Potential interactions caused by drugs also excreted by the renal tubule, such as trimethoprim, are thought to be unlikely [25].

CONCLUSION

On the basis of a currently limited literature a single daily dose of paliperidone ER appears to be effective in treating schizophrenia, maintaining symptom control and preventing recurrence. There appears to be a refined side effect profile compared to risperidone and the absence of effects on glucose and lipids augurs well in any comparison with olanzapine [19]. There are however relatively few research papers about paliperidone and most have been generated by the manufacturers. Independently funded studies would be valuable. Clinical experience and post-marketing data regarding adverse events and particularly prolactin related side effects will need to be monitored however. The clinical experience built up over many years with risperidone would suggest that an improved variant, paliperidone, would have a valuable therapeutic role and that it probably represents an upgrade rather than a wholly novel antipsychotic. There is a welcome prospect of a depot formulation.

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