Graylands Hospital
Drug Bulletin

Paliperidone: Me-Too Drug or Therapeutic Advance?

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Introduction

Paliperidone (Invega®) is the latest atypical antipsychotic approved for use in the treatment of schizophrenia in Australia. Paliperidone is not precisely a novel drug; it is in fact the major active metabolite (9-hydroxy risperidone) of risperidone[1]. This bulletin reviews the pharmacology, pharmacokinetics, efficacy, safety, drug interactions and administration of paliperidone and compares it to other available antipsychotics.

Pharmacology

Paliperidone's mechanism of action is as a dopamine D2, serotonin 5HT2A, histamine H1 and α1- and α2-adrenergic receptor antagonist[1]. It has a low affinity for cholinergic muscarinic receptors[1]. **Table 1** compares the pharmacological profiles of paliperidone with the other atypical antipsychotics. The pharmacological profile of paliperidone predicts its efficacy as well as its adverse effect profile.

Much of paliperidone's pharmacological profile is similar to that of risperidone[2,3]. This occurs for two reasons: firstly, both paliperidone and risperidone have a very similar receptor-antagonist profile. Secondly, because the majority of risperidone is converted to paliperidone, paliperidone is actually responsible for most of the clinical effects of risperidone[3].

Pharmacokinetics

A summary of the major pharmacokinetic properties of paliperidone is listed here; a more complete description is included in the product information. The absolute bioavailability of paliperidone is 28%[4]. The time to steady-state is 4-5 days[4]. Administering paliperidone with food results in a 60% increase in peak concentration of paliperidone and a 54% increase in area under the plasma concentration time curve[4]. However, it is not necessary to administer paliperidone with food[4]. Paliperidone has an apparent volume of distribution of 487L, and approximately 74% of paliperidone is bound to plasma protein[4].

Although *in vitro* studies suggested that paliperidone is metabolised by CYP 2D6 and 3A4 isoenzymes, this was not replicated in *in vivo* studies[4]. Elimination of paliperidone following administration is mainly through the renal route and has a terminal elimination half-life of 23 hours[4].

Table 1: Pharmacological profile of paliperidone compared to other atypical antipsychotics[1,9,13,14]

Drug and usual dose range	5HT2A	D2	M1	α1	H1
Paliperidone 3-12mg	**+++++**	**++++**	**+**	**++++**	**++++**
Risperidone 2-6mg	+++++	++++	-	++++	++++
Clozapine 200-900mg	++++	++	+++	+++	++++
Olanzapine 5-20mg	++++	+++	+++	+++	++++
Quetiapine 150-750mg	++	++	++	+++	+++
Ziprasidone 40-160mg	+++++	+++	-	+++	++++
Aripiprazole 10-30mg	++++	++++ (partial agonist)	-	+++	+++

Affinity for receptors determined by in vitro radioligand competition assays
Key: K_i(nM) >10,000 = -; 1,000-10,000 = +; 100-1,000 = ++; 10-100 = +++; 1-10 = ++++; <1 = +++++.
(The lower the value, the greater the affinity for the receptor)
Note: no available comparison data for amisulpride

Key:
Serotonin blockade (5HT2A)= Improvement of negative symptoms

Dopamine blockade at D2 receptor=
Mesolimbic area= antipsychotic effect
Nigrostriatal tract= extrapyramidal side effects
Tuberoinfundibular area= prolactin elevation
Mesocortical area= worsening of negative symptoms

Muscarinic blockade (M1)= dry mouth, blurred vision, urinary retention, constipation, tachycardia, mitigation of extrapyramidal side effects

Alpha blockade (α1) = postural hypotension

Histamine blockade (H1)= Sedation and weight gain

Formulation

Paliperidone is formulated in an osmotic release oral delivery system (OROS), which is delivered at a controlled rate over 24-hours[1]. The OROS system allows for once-daily dosing and minimises peaks and troughs in paliperidone levels. The controlled release formulation may also be useful in reducing plasma level-dependent adverse effects, such as orthostatic hypotension and extrapyramidal side effects[3]. To preserve the integrity of the OROS tablet, patients should be advised to swallow the tablet whole and not to chew, split or crush the tablet[1]. The outer casing of the OROS tablet passes through the gastrointestinal tract and may appear as an intact 'ghost tablet' in the stool. Patients should be advised of these 'ghost tablets' at the start of therapy, as they are a common, though unnecessary patient concern.

Efficacy evidence

Schizophrenia

The efficacy of paliperidone has been compared to placebo in the treatment of acute schizophrenia in three trials, and in the maintenance treatment of schizophrenia in a further study.

The primary clinical endpoint in the short-term trials was a change from baseline to study end in the Positive and Negative Symptoms Scale (PANSS) total score[5-7].

In the short term-trials, all paliperidone dose groups had significant reductions compared with placebo in total PANSS score and positive- and negative- symptom subscales (see **table 2**)[5-7].

Although the short-term trials had an olanzapine arm, this was to confirm assay sensitivity only[5-7]; the trials were not sufficiently powered to detect differences between the two groups. Conclusions about the comparative efficacy with other antipsychotics cannot be drawn.

Kramer et al assessed the efficacy of paliperidone in preventing recurrence of schizophrenic symptoms. Patients with schizophrenic symptoms that were controlled by 3-15mg of paliperidone daily were randomized to continue paliperidone (N=105) or switch to placebo (N=105)[8]. Time to recurrence of symptoms was significantly longer among patients in the paliperidone group when compared to placebo ($p<0.001$)[8]. Time points at which 25% of patients experienced recurrence were 23 days for placebo and 83 days for paliperidone[8].

Other mental illness

The efficacy of paliperidone has not been assessed in bipolar disorder, in behavioural disturbances in dementia or other psychiatric illnesses.

Safety

The adverse effect profile for paliperidone appears similar to that of risperidone, although the full adverse effect profile for paliperidone will only be established after wider, long-term use in a broader patient population.

No unexpected adverse events occurred in the short-term studies of paliperidone conducted to date[5-7].

Common adverse effects

Common adverse effects reported in the clinical trials with an incidence ≥5% include: tachycardia, headache, somnolence, anxiety, and extrapyramidal disorder including akathisia[1].

QTc prolongation

Pooled data from the three short-term efficacy trials showed that the mean QTc interval for paliperidone-treated patients was not prolonged beyond 5ms and no patient's QTc interval exceeded 500ms at any time, although one patient on 12mg of paliperidone experienced a QTc prolongation by 60ms[1].

Metabolic syndrome

Weight gain, increased blood glucose levels and increased triglycerides have been reported with paliperidone[1]. There is insufficient information to directly compare these incidences with other available antipsychotics.

Seizure disorder

In the pre-marketing trials, the incidence of seizures was similar to that of placebo[1]. However, caution is required in patients with a history of seizures[1].

Other adverse effects

Although the relative risk of developing neuroleptic malignant syndrome or tardive dyskinesia with paliperidone is unknown, it is an inherent risk with all antipsychotics and all patients must be monitored for these adverse effects[1].

Pregnancy and lactation

The safety of paliperidone in pregnancy and lactation has not been established[1]. The Australian Drug Evaluation Committee lists paliperidone as category B3 in pregnancy [1]. Although there is inadequate human data, teratogenicity is not expected, but foetal harm may occur[1].

Drug interactions

Drug interactions with paliperidone have not been systematically evaluated however there is a low likelihood of clinically significant pharmacokinetic interactions[9]. Most clinically significant interactions would involve pharmacodynamic mechanisms.

Pharmacokinetic interactions

Unlike risperidone, paliperidone is not known to inhibit cytochrome P450 2D6, so it is not likely to affect the levels of drugs that are significantly metabolised by this enzyme[1].

Paliperidone is predominantly excreted unchanged in the urine, so inhibition or induction of hepatic cytochrome P450 enzymes by other drugs is not likely to have a significant effect on plasma levels of paliperidone[1].

Paliperidone levels are not likely to be significantly affected by smoking status, as paliperidone is not a substrate for cytochrome P450 1A2[1].

Pharmacodynamic interactions

Caution is required when combining paliperidone with drugs known to prolong the QTc interval[1]. Examples of groups of drugs known to prolong the QTc interval include some antiinfectives, antiarrhythmics and psychotropics. A comprehensive list of drugs that are known to prolong the QTc interval can be found at www.qtdrugs.org [10].

The manufacturers state that caution is required when used with other centrally acting drugs[1].

As with all antipsychotics, paliperidone can antagonise the effects of dopamine agonists such as levodopa that are used in Parkinson's disease. Due to its relative strong affinity for the dopamine D2 receptor, this interaction may be more significant than with some other atypical antipsychotics such as quetiapine or clozapine[9].

Dosing and administration

The usual starting dose for paliperidone is 6mg once daily in the morning[1]. If necessary, the dose can be adjusted by 3mg every five days[1]. The usual effective dose range for paliperidone is 3-12mg daily[1]. The maximum dose is 12mg daily. Paliperidone tablets must be swallowed whole but can be administered without regard to food[1].

Outpatient data from the United States show that the most commonly prescribed doses in practice are between 3-6mg daily[11].

Dose adjustments are not required in patients with mild-to-moderate hepatic impairment, as paliperidone is excreted unchanged in the urine[1].

A starting dose of 3mg daily is recommended for patients with mild-to-moderate renal impairment[1]. For patients with a creatinine clearance of ≥10-<30mL/min, a dose of 3mg on alternate days is recommended[1].

Similar dosing recommendations apply for elderly patients as for adult patients[1].

The safety and efficacy of paliperidone in children and adolescents has not been established and dose ranges are not given.

Place in therapy

The Therapeutic Goods Administration has approved paliperidone for the treatment of schizophrenia including acute treatment and recurrence prevention. It is not approved for treatment-resistant schizophrenia.

The prolonged-release formulation of paliperidone results in reduced plasma level fluctuations when compared to risperidone[1]. It may offer a theoretical advantage over risperidone in patients with mild-to-moderate hepatic impairment or in patients with potentially problematic drug interactions[12].

The lack of direct comparative data with other antipsychotics including risperidone means that any theoretical advantages of paliperidone need to be confirmed in clinical practice.

Availability and pricing

Paliperidone is available on the Pharmaceutical Benefits Scheme (PBS) as a streamlined authority benefit for the treatment of schizophrenia. Invega® tablets are available in 3mg, 6 mg and 9mg strengths with a pack size of 28 with up to five repeats allowable. According to the Graylands drug utilisation data, the mean dose of olanzapine used is 19mg, which has a PBS recovery price of approximately $397[16] and the mean dose of risperidone is 4mg, which has a PBS recovery price of $265[16]. The PBS recovery price for a one-month supply of all strengths of paliperidone is approximately $248[16]. However, an approximately equivalent 12mg dose would have a PBS recovery price of approximately $496[16].

Conclusions

Paliperidone is the active metabolite of risperidone and is classed as an atypical antipsychotic indicated for the treatment of schizophrenia. It has not been directly compared in terms of effectiveness with other antipsychotics. Its theoretical advantages over risperidone need to be confirmed in clinical practice.

Table 2: Results of short-term paliperidone efficacy trials[5-7]					
Study and duration	Placebo (n= Number of patients **Change from baseline PANSS** (SD))	Paliperidone 3mg (n= Number of patients **Change from baseline PANSS** (SD))	Paliperidone 6mg (n= Number of patients **Change from baseline PANSS** (SD))	Paliperidone 9mg (n= Number of patients **Change from baseline PANSS** (SD))	Paliperidone 12mg (n= Number of patients **Change from baseline PANSS** (SD))
Marder et al 6 weeks	n=105 **-8.0** (21.48)		n=110 **-15.7** (18.89)		n=111 **-17.5** (19.83)
Kane et al 6 weeks	n=126 **-4.1** (23.16)		n=123 **-17.9** (22.23)	n=122 **-17.2** (20.23)	n=129 **-23.3** (20.12)
Davidson et al 6 weeks	n=120 **-2.8** (20.89)	n=123 **-15.0** (19.61)		n=123 **-16.3** (21.81)	

Varenicline for smoking cessation in psychiatric patients

Varenicline (Champix®)

Varenicline is the latest medication available to assist in the treatment of smoking cessation.

Varenicline is thought to work by specifically targeting nicotine receptors in the brain, which in turn reduces craving and withdrawal symptoms and decreases the pleasure associated with smoking[1].

It is not a nicotine replacement therapy and does not treat the symptoms of acute nicotine withdrawal following abrupt cessation of smoking[1].

Use in Psychiatric Patients

As pre-registration trials for varenicline were completed in generally healthy, motivated quitters who received regular smoking cessation support and advice[2], the safety and efficacy in smokers with serious psychiatric illness has not been established.

The information received about varenicline's psychiatric adverse effects is through post-marketing experience, mainly from the USA. According to the Food and Drug Administration, "it appears increasingly likely that there is an association between varenicline and serious neuropsychiatric symptoms"[3].

Some of the case reports received are presented below:

A patient with schizophrenia who had been taking varenicline 2mg for 5 days to help her quit smoking suddenly developed exacerbations of schizophrenia. After varenicline was ceased she had no further exacerbations[4].

Varenicline has been reported to induce a manic episode in a 63-year-old male patient with bipolar disorder[5].

In another report, a 41 year old woman with a history of bipolar II disorder started feeling irritable and unsettled three days after starting varenicline 1mg twice daily [6]. These symptoms resolved upon discontinuation of varenicline[7].

Conclusion

The Australian product information lists psychiatric illness as a precaution for varenicline use[1]. Safety and efficacy of varenicline in psychiatric patients has not yet been fully established and it is vital that these patients are monitored for worsening of their illness.

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