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Paliperidone: quo vadis?

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SUMMARY

Paliperidone, the 9-hydroxy metabolite of risperidone, was approved on 20 December, 2006 by the US Food and Drug Administration for the treatment of schizophrenia. It is also being tested for the treatment of bipolar mania. An on-line query of http://www.pubmed.gov and http://www.clinicaltrials.gov for 'paliperidone' and '9-hydroxy-risperidone' was done, along with an examination of poster presentations at scientific meetings held in 2006. Three 6-week pivotal clinical trials of paliperidone extended-release at fixed doses ranging from 3 to 15 mg administered orally once daily in the treatment of acute schizophrenia demonstrated superior efficacy to placebo. A favourable tolerability profile was also evidenced, except for prolactin elevation and dose-related extra-pyramidal effects. A relapse prevention study provides evidence of superiority of paliperidone over placebo in the maintenance of response. Safety has also been assessed in patients with schizophrenia who are 65 years or older. At present there are no studies available that are powered to directly compare paliperidone to other second-generation antipsychotics, including risperidone. With the impending availability of oral risperidone as a generic medication, cost of oral paliperidone will likely become a significant obstacle to its use.

Review Criteria

On-line query of http://www.pubmed.gov and http://www.clinicaltrials.gov for 'paliperidone' and '9-hydroxy-risperidone'. Poster presentations at scientific meetings held in 2006.

Message for the Clinic

Paliperidone, the 9-hydroxy metabolite of risperidone, was recently approved by the US Food and Drug Administration for the treatment of schizophrenia. It is also being tested for the treatment of bipolar mania. An intramuscular depot formulation is being developed as well. Advantages over risperidone are unclear. Cost may become the driving issue regarding its utilisation.

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Introduction

Paliperidone is a second-generation antipsychotic and was approved on 20 December, 2006 by the US Food and Drug Administration for the treatment of schizophrenia. Also known as 9-hydroxy-risperidone, it is the major plasma metabolite of risperidone, a second-generation antipsychotic that was launched commercially in 1994. Risperidone is extensively used, and has received regulatory approval for the treatments of schizophrenia, bipolar mania, and more recently, irritability associated with autistic disorder in children and adolescents. Risperidone was demonstrated in a meta-analysis to be superior to first-generation antipsychotics for the treatment of schizophrenia (1). However, risperidone was inferior to clozapine in a large clinical trial that examined head-to-head multiple second-generation antipsychotics (2). It is anticipated that paliperidone will have an efficacy profile similar to risperidone when tested under the same conditions.

Data sources

Clinical trial information was accessed by on-line query of http://www.pubmed.gov and http://www.clinicaltrials.gov for the search terms 'paliperidone' and '9-hydroxy-risperidone'. No date or language constraints were utilised. Proceedings of the following scientific meetings were searched for paper and poster presentations: 159th Annual Meeting of the American Psychiatric Association, Toronto, ON, Canada, 20–25 May, 2006; 46th Annual Meeting of the NCDEU, Boca Raton, FL, 12–15 June, 2006; 25th Congress of the Collegium Internationale Neuro-psychopharmacologicum, Chicago, IL, 9–13 July, 2006; 19th Congress of the European College of Neuropsychopharmacology, Paris, France, 16–20 September, 2006. Where there are differences between the submitted abstract and the copy of the poster provided, the data from the poster copy is used. To ensure that all publicly available information was collected, a request for information was made to Ortho-McNeil Janssen Scientific Affairs, LLC of Titusville, NJ, USA and was fulfilled on 2 October, 2006.

Mechanism of action and metabolism

Paliperidone is the 9-hydroxy metabolite of risperidone. The pharmacological properties of paliperidone are comparable with risperidone itself (3). It is a monoaminergic antagonist that exhibits binding at

dopamine type 2 and serotonin type 2A receptors (4), as generally expected for members of the class of second-generation antipsychotics. Other potentially important therapeutic receptor actions for risperidone and paliperidone include affinities for serotonin type 2C, 1D and 1A receptors (4,5). The different secondary binding affinities (i.e. other than at dopamine type 2 and serotonin type 2A receptors) for the different second-generation antipsychotics may explain individual patient differences in therapeutic response from drug to drug and from dose to dose (5). Binding affinities may also be helpful in predicting a medication's potential for adverse effects. Paliperidone is active as an antagonist at alpha 1 and alpha 2 adrenergic receptors and at histaminergic 1 receptors, which may explain weight gain, orthostatic hypotension or sedative side effects (5,6). Paliperidone has no muscarinic cholinergic antagonist properties, which would predict a low propensity for causing anticholinergic side effects, including cognitive dysfunction and gastrointestinal disturbances (5).

In the rat, the distribution of paliperidone to the different brain regions was more limited than that of risperidone, and the conclusion was that paliperidone contributes to the *in vivo* activity of risperidone, but to a smaller extent than would be predicted by plasma levels (3). Mean residence times in the frontal cortex and striatum were 4–6 h for risperidone and about 12 h for paliperidone (3). These mean residence times were 3–5 times longer than what was observed in plasma and in the cerebellum (3).

Paliperidone is primarily excreted renally (7), and hepatic metabolism is not the major clearance route. When the immediate release (IR) formulation of paliperidone (1 mg single oral dose) was administered to persons with moderate hepatic impairment, unbound plasma paliperidone concentrations were similar to that observed for healthy subjects (7).

In essence, many patients taking risperidone are already being treated with paliperidone. When measuring plasma levels of risperidone, it is imperative to measure plasma levels of paliperidone, as a substantial percentage of patients may have non-detectable plasma levels of risperidone, yet have measurable amounts of paliperidone (8). Examining the relationship between paliperidone plasma levels and potential effects has been the focus of several studies of risperidone. In one study, there was no correlation between plasma levels of risperidone or paliperidone on antipsychotic response measured by the Positive and Negative Syndrome Scale (PANSS), but active moiety concentrations in plasma were higher in patients who developed clinically significant Parkinsonian symptoms (9). The effects of co-medication of risperidone with carbamazepine or valproate were examined in a pharmacokinetic study in patients with schizophrenia, schizoaffective disorder or bipolar disorder (10). Valproate co-administration did not impact plasma concentrations of risperidone or paliperidone; however, carbamazepine co-administration resulted in statistically significant decreases of paliperidone concentrations. Active moiety concentrations were reduced by approximately 70%, attributed to the induction of CYP3A4 metabolism by carbamazepine (10).

The effect of risperidone and paliperidone on prolactin has also been examined. In a study of 25 patients with psychotic disorders, the plasma concentration of paliperidone, but not risperidone, correlated significantly with increases in plasma prolactin, leading the authors to conclude that paliperidone may play a predominant role in risperidone's effect on prolactin release (11). The investigators attribute this to the different pharmacokinetics of risperidone and paliperidone, namely protein binding being less for paliperidone (77.4% vs. 90.0%) (12) and paliperidone being less lipophilic. In addition, the half-life of paliperidone is substantially longer than that for risperidone (20 h vs. 2–4 h) (13).

Formulations

Several formulations of paliperidone have been tested, including an oral immediate-release formulation, an oral extended-release (ER) formulation, and a depot intramuscular formulation.

Currently available is the oral ER formulation of paliperidone. It uses a patented technology called osmotic-controlled release oral delivery system (14). The ER formulation of paliperidone consists of an osmotically active trilayer core, composed of two drug layers and a push layer (14). The intent is to ensure a gradual rise in the blood concentrations of paliperidone so that a therapeutically effective starting dose can be given. The medication can be administered once daily and it is expected that by reducing the amplitude of the peaks and troughs, which are seen with IR oral therapies in general, it is thought that the risk of adverse effects can be reduced.

Clinical trials

Table 1 lists the clinical trials of paliperidone that have been registered on http://www.clinicaltrials.gov, a repository operated by the US National Institutes of Health and the National Library of Medicine. Of the 22 studies registered, 18 are with patients with schizophrenia (including one study for patients age

65 years and over), one in schizoaffective disorder, and three in bipolar, manic or mixed episodes. Twenty Phase III studies are listed, one Phase II study and one Phase I study. Fifteen studies are using the oral ER formulation of paliperidone, and seven are for the depot intramuscular formulation. According to the registry, seven studies are actively recruiting patients, two have not yet begun, nine are no longer recruiting and four have been completed. There are several more studies that have been done but have not been registered because the requirement for doing so has only recently been mandated in 2005, and then again, is necessary only if publication is desired in a journal that ascribes to standards promulgated by the International Committee of Medical Journal Editors (15,16).

At the time of this review there has been only one published efficacy trial of paliperidone (17). In that study, the efficacy and safety of paliperidone ER was assessed over a 6-week period by comparing fixed doses of 6, 9 and 12 mg administered once daily vs. placebo. Olanzapine 10 mg administered once daily was used as an active control. In total, 628 patients with an acute episode of schizophrenia were randomised at 47 centres in Europe and six centres in India. The primary efficacy outcome measure was change in PANSS total score from baseline to end-point. Average age of the study participants was 37 years; 86% were white, and 52% male. The average age at diagnosis was 27 years and 42% had been hospitalised at least four times. Mean baseline PANSS score was 94. Only 45.6% of the patients randomised to placebo completed the 6-week double-blind period, compared with 65.0% of patients randomised to paliperidone 6 mg, 70.5% of patients randomised to paliperidone 9 mg, 77.7% of patients randomised to paliperidone 12 mg, and 70.3% of patients randomised to olanzapine 10 mg. This translates to number needed to treat (NNT) for completion vs. placebo of 6, 4, 4 and 4 for paliperidone 6, 9, 12 mg and olanzapine 10 mg respectively [for a discussion of NNT and related concepts see Ref. (18)].

The efficacy outcomes demonstrated that paliperidone was efficacious (17). The mean decreases in PANSS total scores were 4.1 for placebo, 17.9, 17.2 and 23.3 for paliperidone 6, 9 and 12 mg respectively, and 19.9 for olanzapine. Thus paliperidone demonstrated statistically significant improvements over placebo at all three doses tested. This was also the case for the factor scores examining positive symptoms, negative symptoms, depression/anxiety, uncontrolled hostility/excitement and disorganisation. Superiority over placebo was evident at day 4 for paliperidone 12 mg and at day 8 for the 6 and 9 mg doses. Responder analyses examining percentage improvement in PANSS as well as improvements in Clinical Global Impression-Severity scores were consistent with the above. Personal and social functioning were also tested using novel scales, and improvements were greater for paliperidone compared with placebo.

Tolerability outcomes demonstrated that paliperidone is reasonably well tolerated (17). Treatment emergent adverse events led to study discontinuation in 7% of those randomised to placebo, 7%, 3% and 6% of those randomised to paliperidone 6, 9 and 12 mg respectively and 7% of those randomised to olanzapine. The most common adverse event that led to discontinuation was tachycardia (2% in the paliperidone 12 mg group vs. 1% in all other groups). Tachycardia itself occurred in 10% of those randomised to placebo, 18%, 14% and 22% of those randomised to paliperidone 6, 9 and 12 mg respectively and 14% of those randomised to olanzapine. The occurrence of serious adverse events was 2% of the placebo group, 4%, 1% and 5% for the paliperidone 6, 9 and 12 mg groups respectively, and 2% for the olanzapine group.

Mean plasma prolactin levels increased among patients receiving paliperidone, from a baseline of 17.4 to 45.3 ng/ml for the men, and from 38.0 to 124.5 ng/ml for the women. The changes in plasma prolactin for each dose of paliperidone were not reported, nor were the percentages of patients who experienced categorical shifts from a normal plasma prolactin level to an abnormally high level. Mean prolactin levels decreased from baseline to end-point in both men and women in the placebo and olanzapine groups. Potentially prolactin-related adverse events were reported by 1% of participants (three men, one in each of the paliperidone arms), and four women (one in each of the active treatment arms).

The frequency of movement disorder-related adverse events was similar between paliperidone 6 mg and placebo, but more patients in the 9 and 12 mg groups reported these than those in the placebo group. This is consistent with what was observed with the Simpson Angus Scale (SAS), Barnes Akathisia Scale (BAS), and the Abnormal Involuntary Movement Scale (AIMS). At end-point the use of anticholinergic medication was 6% in the placebo group, 11%, 17% and 22% in the paliperidone 6, 9 and 12 mg groups respectively, and 8% in the olanzapine group. There were no glucose-related adverse events or substantial changes in glucose, insulin, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol or triglycerides for any of the groups. Weight increase ≥ 7% was seen in 2% of the placebo group, 5%, 7% and 3% of the

Table 1 Paliperidone clinical trials registered at http://www.clinicaltrials.gov*

ClinicalTrials.gov identifier	Duration (weeks)	Phase	Condition	N	Paliperidone doses and comparator	Comments
NCT00299715	3	III	Bipolar, manic or mixed	464	ER 3, 6 or 12 mg/day vs. placebo	Began 1/2006, USA and international sites. Recruiting
NCT00309699	Acute 3, total 12	III	Bipolar, manic or mixed	475	ER 3–12 mg/day vs. quetiapine 400–800 mg/day vs. placebo	Began 4/2006, USA and international sites. Recruiting
NCT00309686	6	III	Bipolar, manic or mixed, and taking lithium or valproate	296	ER 3–12 mg/day vs. placebo, added to lithium or valproate	Began 4/2006, USA and international sites. Recruiting
NCT00105326	?	II	Schizophrenia and schizophrenia-related insomnia, otherwise stable	?	ER 9 mg/day vs. placebo	Began 2/2005. Completed. Conducted in a total of nine sites in France, Poland and Romania. Studied sleep architecture using polysomnography
NCT00119756	?	III	Schizophrenia	282	PD dose not listed	Began 6/2005. Study sites not listed. No longer recruiting. Studies safety and tolerability comparing injection in shoulder vs. buttock muscles
NCT00397033	6	III	Schizoaffective disorder, psychotic disorder	315	ER 6 vs. 12 mg/day vs. placebo	Not yet recruiting
NCT00334126	Acute 2, total 6	III	Schizophrenia	395	ER 9–12 mg/day vs. quetiapine 600–800 mg/day	Began 5/2006, USA sites. Recruiting
NCT00210548	13	III	Schizophrenia	376	PD 50, 100 or 150 mg eq vs. placebo, 4 injections on days 1, 8, 36 and 64	Began 4/2005, USA and international sites. Recruiting
NCT00210769	52	III	Schizophrenia	350	Following a 6-week double-blind study comparing ER 6 or 12 mg/day vs. olanzapine 10 mg/day, subjects received open-label ER 3–12 mg/day open-label	Began 1/2004. Study sites not listed. No longer recruiting
NCT00210717	52	III	Schizophrenia	700	PD 25–100 mg eq every 4 weeks vs. risperidone depot 25–50 mg every 2 weeks	Began 2/2005. Study sites not listed. No longer recruiting
NCT00257023	8	II	Schizophrenia	45	Open-label ER 3, 9 or 15 mg/day for 6 weeks	Began 2/2005. Done in Japan. No longer recruiting
NCT00086320	?	III	Schizophrenia	?	ER dose not listed vs. placebo, with optional open-label extension	Began 10/2004, USA sites. Completed
NCT00078039	6	III	Schizophrenia	595	ER 6, 9 or 12 mg/day vs. olanzapine 10 mg/day vs. placebo, with optional open-label extension	Began 3/2004, international sites. No longer recruiting
NCT00083668	6	III	Schizophrenia	595	ER 3, 9 and 15 mg/day vs. olanzapine 10 mg/day vs. placebo, with optional open-label extension	Began 3/2004, USA and international sites. No longer recruiting
NCT00073320	?	I	Schizophrenia	72	PD open-label pharmacokinetic study of injections in the arm or buttock	Began 8/2003. Done in Texas, USA. Completed
NCT00085748	6	III	Schizophrenia, age ≥ 65 years	105	ER flexible-dose (details not listed) vs. placebo, with optional open-label extension	Began 7/2004, international sites. No longer recruiting
NCT00350467	6	III	Schizophrenia	300	ER 3–12 mg/day vs. olanzapine 5–15 mg/day	To be done in China. Not yet recruiting
NCT00077714	?	III	Schizophrenia	440	ER doses not listed	Begun 2/2004, only one USA site listed. Completed
NCT00396565	6	III	Schizophrenia	329	ER 6 mg/day vs. olanzapine 10 mg/day vs. placebo	Begun 6/2006, Japan. Recruiting
NCT00111189	?	III	Schizophrenia	640	PD doses not listed	Begun 3/2005, USA and international sites. Recruiting
NCT00101634	?	III	Schizophrenia	480	PD 25, 50 or 100 mg eq vs. placebo	Begun 12/2004, USA and international sites. No longer recruiting
NCT00147173	?	III	Schizophrenia	376	PD 50, 100 and 150 mg eq vs. placebo	Begun 6/2005, USA and international sites. No longer recruiting

*Accessed 24 November, 2006. ER, extended release; PD, palmitate depot.

paliperidone 6, 9 and 12 mg groups respectively, and 13% of the olanzapine group. There were no instances of patients randomised to paliperidone developing prolonged QT intervals as measured by electrocardiogram.

There are two other short-term efficacy studies of paliperidone ER for acute schizophrenia that have been presented as posters, and hence not subject to peer review (19,20). They are similar in design to the study described above in that they are of 6-week duration, placebo-controlled and used olanzapine 10 mg/day as an active control (17). All active treatment arms demonstrated superiority over placebo in terms of reductions in PANSS total scores. The highlights are presented in Table 2, and contrast all three of these pivotal trials.

The safety and efficacy of flexible doses of paliperidone ER in patients with schizophrenia age 65 years or older was tested in a 6-week placebo-controlled clinical trial and presented as a poster (21). This is of interest because it would be expected that older people would be more sensitive to adverse effects of medications. A total of 114 patients were randomised to receive paliperidone 6 mg or placebo once daily. After 7 days, patients could receive flexible dosing in the range of 3–12 mg daily, in 3 mg dose increments. Mean age was 70 years. Mean modal paliperidone daily dose was 8.3 mg. Completion rates were high: 68% for placebo and 84% for paliperidone (NNT 7). Study discontinuation because of adverse events occurred in 7% of the paliperidone group and 8% of the placebo group. Serious adverse events occurred in 3% of the paliperidone group and 8% in the placebo group. The most common adverse event was tachycardia, reported in 16% of the paliperidone group and in none of the patients receiving placebo. Median global scores on the SAS and median AIMS total scores showed no change from baseline in either treatment group. Akathisia, as measured by the BAS, was absent in 85.5% of the paliperidone patients and in 86.8% of the placebo patients at end-point. No substantial changes in mean glucose or mean bodyweight were noted. Efficacy measures were secondary in this study. Patients receiving paliperidone had greater improvement in PANSS total scores from baseline to end-point compared with patients receiving placebo. Responder analysis (response defined as an improvement in the total PANSS score by at least 30% from baseline to end-point) revealed response rates of 38% for paliperidone and 29% for placebo (NNT 12).

A small study ($N = 36$) of paliperidone ER vs. placebo was conducted at nine sites in Europe among patients with schizophrenia to examine changes in sleep architecture. The results were presented as a poster (22). Patients with schizophrenia and schizophrenia-related insomnia, but without signs of acute psychosis, were randomised to receive paliperidone 9 mg or placebo for 2 weeks. Improvements in sleep continuity were noted for paliperidone vs. placebo, including mean total sleep time and decreases in latency to sleep onset.

Once a patient with acute schizophrenia is stabilised, the goal of treatment is to prevent relapse. Paliperidone's potential utility for this was examined in a double-blind placebo-controlled trial, and presented as a poster (23). A total of 530 patients with acute schizophrenia were enrolled and began an 8-week open-label run-in phase where they received a starting daily dose of paliperidone 9 mg. Increases of 3 mg could occur every 7 days (maximum dose 15 mg daily). Decreases of 3 mg were permitted at any time if there were tolerability problems. The run-in phase was followed by a 6-week stabilisation phase where the fixed dose established in the run-in phase was continued. The poster did not specify the specific response criteria for patients to be eligible to enter the stabilisation phase. A total of 312 patients entered the stabilisation phase and 207 patients subsequently entered the double-blind phase where they were randomised to receive placebo or paliperidone at the dose they were receiving in the stabilisation phase. The poster did not specify the specific response criteria for patients to be eligible to enter the double-blind phase. Participation in the double-blind phase was to be of variable duration, and would continue until the patient experienced a recurrence (defined as hospitalisation, specified increase in PANSS, specified dangerous behaviour or specified worsening on the Clinical Global Impression-Severity scale) or until the study was terminated. The poster does not indicate how the quickly patients were converted from active drug to placebo once they were randomised to placebo. A prespecified interim analysis was performed after 43 recurrence events, and the study was terminated on the basis of significant efficacy results. Recurrence occurred more swiftly for patients randomised to placebo – 25% of patients experienced a predefined recurrence at 23 days with placebo vs. 68 days with paliperidone (Kaplan–Meier, $p < 0.001$). Overall, recurrence occurred in 52% of patients on placebo vs. 22% of patients receiving paliperidone (NNT 4).

Post hoc analyses

Several *post hoc* analyses combining the datasets from the three acute schizophrenia trials (17,19,20) have been presented as posters (24–28). They have focused

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