CASE REPORT

Efficacy and safety of once-monthly paliperidone palmitate long-acting injection in an elderly patient with schizophrenia

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Accepted 10 August 2015

SUMMARY

We present detailed data on the efficacy and safety profile of paliperidone palmitate once-monthly long acting injectable (PP1M-LAI) in the treatment of schizophrenia in an elderly Caucasian woman. PP1M-LAI was initiated with starting doses of 150 and 100 mg on treatment days 1 and 8, respectively. Subsequent 100 mg doses of PP1M-LAI were then administered at 4-weekly intervals. The primary efficacy variable was the change in Positive and Negative Syndrome Scale (PANSS) total score from baseline. Safety assessment variables included assessment of treatment emergent adverse events, clinical laboratory tests, vital sign measurements, ECG, Calgary Depression Scale for Schizophrenia (CDSS), mini-mental status examination, Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), Simpson-Angus Scale for the Assessment of Extrapyramidal Side Effects (SAS) and WHO Quality of Life—BREF (WHO-QOL-BREF). The aforementioned variables were all monitored for changes from baseline over a period of 28 weeks. A reduction of PANSS total score was noted over the 28 weeks, demonstrating the efficacy of PP1M-LAI for the treatment of schizophrenia in our patient. Improvements were also noted in the BARS score, SAS score and WHO-QOL-BREF. Negative findings were observed with regard to several pre-established safety variables such as blood glucose levels, prolactin levels, QTC intervals and weight. Overall, the addition of PP1M-LAI to the treatment regime improved the control of psychotic symptoms. However, iatrogenic consequences arising from the use of PP1M-LAI need to be considered and balanced against the primary efficacy of the medication.

BACKGROUND

Schizophrenia is a debilitating lifelong illness characterised by delusional thinking, the presence of auditory and visual hallucinations, thought disorder and changes in affect, drive and motivation. It is disruptive to, and impacts negatively on, cognition and social functioning. The underlying pathophysiology is not well understood and treatment options are of limited efficacy, extending only to the management of symptoms.

Once-monthly paliperidone palmitate long-acting injectable (PP1M-LAI) is a relatively new antipsychotic that has been approved for the acute management and maintenance treatment of schizophrenia in adults. It is one of three second-generation LAIs that are widely available for the treatment of schizophrenia in Australia—the other

two being risperidone-LAI and olanzapine-LAI. Although its mechanism of action is currently unknown, it is widely thought to have similar pharmacodynamics to risperidone.^{1 2}

In randomised controlled trials, PP1M-LAI has demonstrated efficacy in the treatment of schizophrenia, as evaluated using the Positive and Negative Syndrome Scale (PANSS).^{1–3} Like other second generation LAIs, paliperidone palmitate has been associated with an improved side effect profile compared to first generation LAIs and has demonstrated non-inferiority to existing second generation antipsychotic depots in terms of efficacy and adverse event (AE) profile.^{4 5} PP1M-LAI offers several potential advantages over existing depots in terms of drug administration and tolerability. Maintenance doses of PP1M-LAI are administered every 4 weeks as opposed to fortnightly, as is the case with most other LAIs, which is beneficial for patients with treatment-adherence issues. PP1M-LAI can be administered without oral supplementation when initiating treatment or changing doses, and there is minimal hepatic metabolism, resulting in potentially fewer drug interactions. Additionally, there are fewer concerns over post-injection syndrome; there is also the lack of need for refrigeration.⁶

While the efficacy and AE profile of PP1M-LAI is favourable, this is primarily based on data collected in adults. To date, a dearth of work has been conducted in an aged population and it remains unclear whether these data are directly applicable to a population aged over 65 years. This population is likely to have a longer history of illness, major comorbidities and is likely to experience polypharmacy.

Singh has reported the use of PP1M-LAI in an elderly schizophrenia patient, where it was found to be less efficacious in contrast to risperidone-LAI.⁶ It is unclear whether this outcome was idiosyncratic or typical of an elderly population.

In this case report, we present detailed data on the efficacy and safety profile of PP1M-LAI in an elderly patient. The data presented in this case report will add to the body of knowledge of what we could expect to observe in an elderly population.

CASE PRESENTATION

We describe a case of a 68-year-old Caucasian woman with a 45-year history of treatment-resistant schizophrenia. She had undergone over 30 hospital admissions, many of which had been involuntary and prolonged up to 4–6 months. Over the years, the

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To cite: Rama Raj P, Lewis M, Macfarlane S. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2015-212149

patient had exhibited a significant history of impaired insight, non-compliance to treatment regimes, poor engagement with psychiatric services and self-harming behaviour secondary to her delusions.

Despite currently being managed on a combination of clozapine (250 mg) and zuclopenthixol (400 mg) with augmentation from sodium valproate (1000 mg), her control of her psychotic symptoms remained fluctuant with frequent relapses. Her relapses often encompassed grandiose and persecutory delusions, sexually disinhibited behaviour and an elevated irritable affect. They were usually secondary to alcohol bingeing and non-compliance with medications, particularly with the fortnightly zuclopenthixol injections which she found to be intrusive and a major source of discomfort.

Given the refractory nature of her current symptoms, a review of her medications was undertaken. A clinical decision was subsequently made to replace zuclopenthixol-LAI with an equivalent dose of PP1M-LAI with an aim to enhance her quality of life without precipitating a decline in her mental state.

INVESTIGATIONS

Investigations, with regard to this case report, involved the assessment of primary and secondary outcomes, are recounted in the 'Treatment Section'.

TREATMENT

PP1M-LAI was initiated with starting doses of 150 and 100 mg on treatment days 1 and 8, respectively. Subsequent 100 mg doses of PP1M-LAI were then administered at 4-weekly intervals. These treatment dosages were in accordance with evidence-based guidelines for rapidly achieving therapeutic plasma concentrations.⁷ The concomitant use of clozapine and sodium valproate was also permitted to continue.

The efficacy and safety profile of PP1M-LAI was evaluated over a 28-week period from baseline through to end point assessment. The primary efficacy variable was the change in PANSS total score from baseline. Safety assessment variables included assessment of treatment-emergent AEs, clinical laboratory tests, vital sign measurements, ECG, Calgary Depression Scale for Schizophrenia (CDSS), mini-mental status examination, Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), Simpson-Angus Scale for the Assessment of Extrapyramidal Side Effects (SAS) and WHO Quality of Life-BREF (WHO-QOL-BREF).

Baseline values of efficacy and safety variables were recorded prior to the initiation of the starting dose on day 1. Subsequent changes in these variables were monitored for and recorded at 4-weekly intervals from week 4 to week 12, and at 8-weekly intervals from week 12 to week 28. The results are shown in [table 1](#).

OUTCOME AND FOLLOW-UP

There was reduction in the PANSS total score from baseline to end point over the course of 28 weeks. Reductions in the PANSS score were noted as early as week 4 and maintained a trajectory of improvement. The patient's end point PANSS score of 49 was well below the mean PANSS score observed in schizophrenic individuals,⁸ and demonstrates that PP1M-LAI was effective in treating schizophrenia in this patient.

Improvements were also noted in three of the safety assessment variables. The baseline BARS score of 3 had dropped to 0 by week 4, a score that was subsequently sustained through to the end point assessment at week 28. This signalled a complete resolution of the patient's akathisia, which was possibly related

to the immediate past use of zuclopenthixol. Given the patient's past poor tolerance of antipsychotics due to motor side-effects, the lack of akathisia associated with PP1M-LAI use was certainly a favourable outcome. The SAS, which assesses for drug-induced Parkinsonism, also signalled a marked improvement over the 28-week period, with a reduction from a baseline score of 8 to an end point score of 3. This finding is consistent with current clinical evidence that associates PP1M-LAI with a lower incidence of extrapyramidal side effects.^{4 5}

The patient's quality of life, as measured with the WHO-QOL-BREF, improved over the 28-week period. Her end point scores in each of the four domains (physical, psychological, social and environmental) evaluated, were well above the national average among Australians, with the most prominent improvements observed in the social and psychological domains.⁹ This correlated with her clinical notes where treating staff observed a steady improvement in her mental state and a reduction in relapse episodes through the observation period. There were no changes to baseline readings of CDSS and AIMS observed over the course of the follow-up period.

Despite the positive data findings on efficacy, movement-related disorders and overall quality of life, safety evaluations yielded less favourable findings with regard to several pre-established safety variables. Hyperglycaemia is regarded as a potential side effect of PP1M-LAI use and laboratory findings demonstrated a substantial increase in fasting blood glucose levels from baseline over the 28-week period. Considering the patient's underlying diabetes and lack of compliance with diabetes medications, PP1M-LAI use seemed to have further exacerbated her poor blood glucose control. This is consistent with evidence from clinical trials where treatment-emergent glucose related AEs, though uncommon, have been observed.¹⁰ As such, PP1M-LAI can be used in schizophrenic patients with comorbid diabetes mellitus, however, it should always be accompanied by regular blood glucose monitoring.

Abnormally elevated prolactin levels were also noted over the 28-week period. Hyperprolactinaemia is a well-established side effect associated with antipsychotic medications as a result of their dopamine antagonism and is known to be associated with higher rates of cardiovascular disorders, osteoporosis, breast cancer and depression, particularly in postmenopausal women.¹¹ Though none of these complications had manifested in our patient as of week 28, her future management should entail careful screening for these complications given her known risk factors of diabetes, postmenopausal female gender, and her age, and we would extend these recommendations to others being treated with PP-LAI.

QTc prolongation was another side effect associated with PP1M-LAI use in our patient. Her baseline QTc reading of 446 gradually increased over the 28-week follow-up period to a final reading of 488. This finding is consistent with existing work that established QTc prolongation as a common-side effect of most antipsychotics, and one that is typically less pronounced in PP1M-LAI in contrast to other injectable antipsychotics.¹² By the final assessment at week 28, no ventricular arrhythmias associated with QTc prolongation had been detected.

Weight gain was also noted in the patient, as a result of PP1M-LAI use. The onset of weight gain (also common to other antipsychotics) was noted as early as week 8, where there was an increase from baseline weight of 91.6–95.2 kg. Mild macrocytosis was also noted as an AE at week 28. However, neither its significance nor its relationship to the study drug was clear. A longer assessment period would have been required to investigate the relationship of this finding to PP1M-LAI use.

Table 1 Efficacy and safety variables in assessing PP-LAI use

Variables	Assessment findings						
	Normal values	Baseline*	Week 4	Week 8	Week 12	Week 20	Week 28
PANSS	–	67	<u>57</u>	<u>53</u>	<u>51</u>	<u>53</u>	<u>49</u>
CDSS	–	0	0	0	2	0	0
MMSE	–	27	27	26	29	27	27
AIMS	–	0	0	0	0	0	0
BARS	–	3	<u>0</u>	<u>0</u>	<u>0</u>	<u>0</u>	<u>0</u>
SAS	–	8	<u>5</u>	<u>3</u>	<u>5</u>	<u>2</u>	<u>5</u>
WHO-QOL BREF (range 4–20)	–	D1: 10 D2: 11 D3: 5 D4: 11	D1: <u>18</u> D2: <u>13</u> D3: <u>7</u> D4: <u>19</u>	–	–	D1: <u>17</u> D2: <u>18</u> D3: <u>17</u> D4: <u>15</u>	D1: <u>15</u> D2: <u>17</u> D3: <u>20</u> D4: <u>16</u>
Fasting blood glucose (mmol/L)	(4.0–6.0)	9.5	14.7	6.9	14.6	12.6	13.4
Fasting total cholesterol (mmol/L)	(0.0–5.5)	3	3	2.9	3	3.1	3.2
Fasting HDL (mmol/L)	(0.9–2.2)	1.2	1.2	1	1.2	1.2	1
Fasting LDL (mmol/L)	(<3.4)	0.7	0.9	0.8	1.2	1.3	1.2
Fasting triglycerides (mmol/L)	(0.5–2.0)	2.5	1.9	2.3	1.2	1.3	2.2
Prolactin (μmol/L)	(59–619)	514	1119	1036	878	1201	1025
Urea (mmol/L)	(3.0–10.0)	5.1	5.2	5.8	4.9	6.9	6.6
eGFR (mL/min)	(>60)	>90	>90	>90	>90	81	>90
Hb (g/L)	(11.5–16.5)	13	12.2	12.2	11.6	11.8	12.2
WC (×10 ⁹ /L)	(4.0–11.0)	5.7	4	6.7	5.2	5.2	5.7
Platelets (×10 ⁹ /L)	(150–450)	244	243	260	292	313	355
Weight (kg)	–	91.6	–	95.2	–	96.4	94.2
Blood pressure—supine (mm Hg)	–	155/102	–	148/85	–	138/88	142/67
Blood pressure—standing (mm Hg)	–	155/94	–	143/74	–	140/105	149/95
Pulse (bpm)	60–100	102	–	91	–	97	97
ECG (QT _c interval)	<470	446	–	474	–	473	488
Other adverse events	–	–	–	–	–	–	Mild Macrocytosis (MCV=99)

Bold italics indicate deterioration from baseline.

Bold Underline indicates improvement from baseline.

*Day 1 - prior to 1st starting dose of 150mg.

AIMS, Abnormal Involuntary Movement Scale; BARS, Barnes Akathisia Rating Scale; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; Hb, haemoglobin; LDL, low-density lipoprotein; MMSE, mini-mental status examination; PP-LAI, paliperidone palmitate long acting injectable; PANSS, Positive and Negative Syndrome Scale; SAS, Simpson-Angus Scale for the Assessment of Extrapyramidal Side Effects; WHO Quality of Life-BREF; WHO-QOL-BREF.

Overall, the addition of PP1M-LAI to this patient's treatment regime seemingly improved the control of her psychotic symptoms as assessed by the efficacy variables of this case study and by her clinical records, which documented the improvement in her mental state and reduction in relapses. There were some

iatrogenic consequences arising from the use of PP1M-LAI, and it is important that these are considered and balanced against the primary efficacy of the medication. Given the ever-present need to increase treatment options in schizophrenia, this case study serves to highlight the valuable role that PP1M-LAI could potentially play in treating the elderly population. However, this case study also serves to underline the need for larger studies of PP1M-LAI in elderly populations to better elucidate the safety profile of the drug in this vulnerable group.

Contributors SM and ML conceived and designed the study, and contributed to manuscript preparation. PR was primarily responsible for manuscript preparation.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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Learning points

- ▶ Given that the addition of paliperidone palmitate once-monthly long acting injectable (PP1M-LAI) to our patient's treatment regime seemingly improved the control of her psychotic symptoms, clinicians could potentially turn to PP1M-LAI as an alternative antipsychotic in treating the elderly population who are not able to tolerate more conventional antipsychotics.
- ▶ Iatrogenic consequences (ie, QTc prolongation, hyperglycaemia) arising from the use of PP1M-LAI must be considered and balanced against the primary efficacy of the medication.
- ▶ This case study underlines the need for larger studies of PP1M-LAI in elderly populations to better elucidate the safety profile of the drug in this vulnerable group.

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