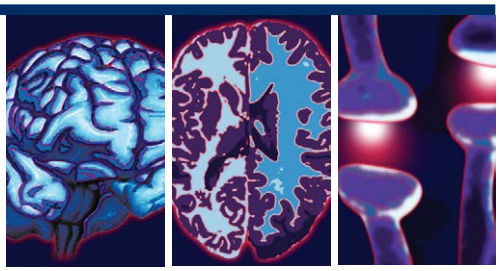

Improvement of Behavioural Disorders in a Sample of Persons with Intellectual Disability after Administration of Paliperidone Palmitate

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ABSTRACT

Objective

Behavioural problems are common in people with an intellectual disability (ID). Psychopharmacological treatments include several drug groups such as antiepileptics, antidepressants, and benzodiazepines, although the most extensively used are antipsychotics, especially risperidone. However, there is little or no literature on the metabolite of its monthly administration – paliperidone palmitate. The objective of this study was to assess the efficacy and tolerability of paliperidone palmitate when administered monthly to treat the behavioural alterations associated with ID.

Methods

This was a prospective, observational, open-label, 3-year duration study on adults with intellectual disabilities (DSM-V criteria) and associated behavioural disorders who had paliperidone palmitate added to their usual treatment. Pre-treatment and 6 months after starting the treatment, the participants were given a full blood chemistry panel, and scored on the Aberrant Behaviour Checklist (ABC) and the UKU side effects scales.

Results

The sample consisted of 34 participants, with a mean age of 40.35 years (18-62), and 64.7% of them had some concomitant medication at baseline. The mean monthly dose of paliperidone palmitate was 116.17 mg (75-200 mg). There were statistically significant improvements in all 5 subscales of the ABC scale (being especially strong for irritability and hyperactivity) and in certain of the metabolic parameters. The treatment was withdrawn in one case due to amenorrhea.

Conclusions

Paliperidone palmitate was associated with significant improvements in behavioural problems associated with intellectual disability, and was well tolerated. Further studies are necessary to establish its efficacy and tolerability for this specific population.

Keywords

Intellectual Disability, Antipsychotics, Paliperidone Palmitate, Risperidone, Behavioural Problem, Hyperprolactinemia, Irritability

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Introduction

Intellectual disability (ID) is defined as abnormal intellectual functioning which originates during the period of development. It has multiple potential etiologies including genetic defects and perinatal injury [1]. According to DSM-V [2] for the diagnosis of intellectual disability or intellectual development disorder the following 3 criteria must be met: intellectual function impairment as confirmed through clinical assessment and individualised standardised intelligence tests; deficiencies in adaptive behaviour; and onset during the period of development. The DSM-IV-TR [3] used IQ to determine whether an individual was intellectually disabled, with values less than 70 being included in the range of disability. Depending on its severity, intellectual disability can be divided into mild, moderate, severe, and profound [2].

Almost all mental pathologies are between 3 and 4 times more frequent in persons with intellectual disabilities than in healthy individuals [3], and more than 50% of them present an additional psychiatric diagnosis, with behavioural disorders being common [4]. In their sample of 1023 participants with ID, Cooper et al. [5] found that just 22.5% of them had no associated psychiatric diagnosis, with this situation being more frequent in women (26%) than in men (19.6%). The behavioural alterations in ID can vary greatly. They include self- and hetero-aggression, impulsiveness, irritability, restlessness, disobedience, social withdrawal, inter alia. Psycho-pharmacological treatment of these behavioural disorders in ID for both adults [6-8] and children [9,10] includes different drug groups – antiepileptics, antidepressants, benzodiazepines, and, above all, antipsychotics. Among the antipsychotics, risperidone seems to have had the most evidence in favour of its use, although its possible adverse side effects mean that it should be administered with caution [11-13]. In a 2011 study of 202 participants with ID [7], 68% were concomitantly taking antipsychotics, 42% antidepressants, 39% antiepileptics, and 25% benzodiazepines, with, among those taking antipsychotics, risperidone being the most commonly used (48%), followed by olanzapine (18%).

Although risperidone has been shown to be effective in treating the behavioural alterations in ID, its tolerability, and especially its interactions with other drugs [14] make its use problematic in a population which, as indicated above, is prone to being polymedicated. Monthly administration of the antipsychotic paliperidone palmitate has been shown to be an effective and well tolerated treatment for schizophrenia and schizoaffective disorder [15]. The fact that it has little hepatic metabolism [16] would favour its use in polymedicated populations, with the added advantage that its monthly administration would improve therapeutic compliance. Nonetheless, despite its being the active metabolite of risperidone, in the literature we could find hardly any reference to its use for behavioural disorders associated with ID.

Kowalski et al. [17] published a case of a 5-year-old boy with autism who, after 3 months of treatment with paliperidone palmitate, experienced significant improvement on the Aberrant Behaviour Checklist (ABC) and the Clinical Global Impression (CGI) rating scales. The treatment was well tolerated and the only noticeable adverse effect was increased appetite. The researchers concluded by suggesting that paliperidone palmitate be considered as a treatment option for children who do not tolerate oral medication.

There is information regarding its use in other pathologies that may present behavioural alterations. Palomares et al. [18] published a study describing its use in 16 subjects diagnosed with borderline personality disorder who had impulsive-aggressive symptoms which had not improved with the daily administration of antipsychotics. This 12-week observational study showed statistically significant improvements in both symptoms and functionality, although the treatment had to be withdrawn for 3 of the subjects because of galactorrhea. There was also a reduction in the consumption of other antipsychotics (from 56% to 25%) and of benzodiazepines (from 81% to 56%).

There is some information about its oral use in ID [19] and in subjects with autism and associated irritability and behavioural alterations [14,20]. These last two studies reported statistically significant improvements on all the ABC subscales and on CGI-I. The drug was also well tolerated. Fernández-Mayoralas et al. [21] described an improvement in irritability and overall clinical impression with the use of paliperidone. Their sample consisted of 18 children and adolescents with severe and excessive irritability in the context of a generalised developmental disorder or attention-

deficit hyperactivity disorder who had previously responded inadequately to risperidone. Those workers also noted the better tolerability of paliperidone compared to risperidone.

The main objective of the present work was therefore to redress the absence of studies of treating the ID population with the antipsychotic paliperidone palmitate. In particular, the two research questions were whether the introduction of this drug in the treatment of a group of individuals with ID and secondary behavioural alterations would significantly improve their ratings on the different ABC subscales, and how well they would tolerate it.

Material and Methods

■ Participants

The participants were from the health area of Zafra-Llerena, in the province of Badajoz (Spain) covered by the Extremadura Health Service. The 3 outpatient psychiatrists of this area provided all the data since none of the subjects were inpatients. With respect to their residence, the subjects were either treated at home, or at a care centre full (24 hours, 7 days a week) or part time (from 09:00 to 17:00, Monday to Friday). They were categorised in accordance with whether their home environment was urban or rural (depending on the town or village's population size being greater or less than 15 000 inhabitants, respectively), by sex, and by age (under 30 years of age, from 31 to 45, from 46 to 60, and over 60).

The sample participants were recruited consecutively over 3 years, from June 2013 to June 2016. The inclusion criteria were: diagnosed with ID (mild, moderate, or severe) in accordance with the DSM-V criteria [3], presenting secondary behavioural alterations requiring psycho-pharmacological treatment, being of at least 18 years in age, undergoing treatment by their reference mental health team, and having no other mental illness codifiable on Axes I or II.

The ID diagnosis had been made in childhood, and since then the participants' IQ had been evaluated by means of different psychometric tests. The behavioural alterations comprised: hetero-aggression, screaming, tantrums, impulsiveness, irritability, restlessness, disobedience, lack of response to the different programs of the centre or not participating in them, throwing things, unexpectedly going out of the centre, little interaction with others, etc. The decision as whether to take as first choice a long-acting injectable (LAI), in this case paliperidone palmitate, was made by the psychiatrist responsible for each participant. Nevertheless, it was observed that sometimes family members or especially the staff at the subject's care centre wanted this to be the choice because of the great improvement they had observed in other persons with ID already taking it. Previously the participants might not have responded to one or more psycho-pharmacological treatments. All the treatment options were explained to their legal guardians who gave their written consent for the subject to receive treatment with paliperidone palmitate.

The study was carried out in accordance with the norms and objectives of the Declaration of Helsinki, adopted at the 18th General Assembly of the World Medical Association (Helsinki, Finland, June 1964) and its subsequent revisions. The exclusive use of the data for the purpose of this research is framed within Article 11 of Law 5/92, and therefore did not require the informed consent of the participants for the transfer of their personal data. The study was reviewed and approved by the corresponding Area Ethical Committee.

■ Study design

This was a prospective, observational, open-label study in which an intervention was performed with a drug without randomization or the presence of a control group. The sample comprised persons with ID who were recruited consecutively. Measurements of the outcome of the variables were made on the same individual after a period of 6 months treatment.

■ Procedures

In the baseline visit, a full blood panel was obtained including biochemistry, hemogram, coagulation, thyroids, prolactin levels, vitamin B12, and folic acid. Aman's ABC scale [22] and the UKU side effects scale [23] were administered, and the different sociodemographic data were registered. The medication they were taking at that time was classified into 4 groups for the subsequent analysis: antipsychotics, antiepileptics, benzodiazepines, and antidepressants. All the antipsychotics were second generation. The antiepileptics had been prescribed with an anti-impulsive purpose. Modifications were made to this prior treatment, but they were slight, and only with the reduction or withdrawal of no more than one of the psycho-

pharmaceuticals they were taking so as to better see the real influence of paliperidone palmitate. By residence, they were divided between those who lived full-time or part-time at a care centre and those who lived at home. The scales were administered by the subjects' psychiatrists from both the information acquired in the clinical interview and that provided by the family members, caregivers, or psychologists who were in direct contact with the subject.

In a second visit after 3 months, the effectiveness and possible appearance of side effects were assessed in case it was necessary to withdraw or modify the treatment. In a third (final) visit after 6 months, a new full blood panel was taken and the same scales were again administered.

■ Evaluation

Aman's ABC scale [22] was used to evaluate the behavioural alterations pre- and post-treatment. This scale is designed to assess the effects of medication or other treatments on subjects with ID, and to study their associated behavioural and psychopathological problems. It comprises 58 items that describe various behavioural problems, corresponding to 5 dimensions: irritability-agitation-crying (15 items), lethargy-withdrawal (16 items), and stereotypy (7 items), and hyperactivity-disobedience (16 items), and loquacity (inappropriate speech) (4 items). Each item is valued from 0 (does not present this problem at all) to 3 (important problem), assessing the behaviour of the individual during the previous 4 weeks. The scale was validated by means of a factor analysis of the scores obtained with a group of 927 persons with ID. This scale does not have a diagnostic capacity. Although there are other scales that assess behavioural changes, we opted for the ABC scale because it is the most extensively applied in the international literature as useful to assess post-intervention changes in behaviour, especially for psycho-pharmacological interventions [14,17,24] and because it is easy to apply even for personnel with minimal knowledge in the field.

The UKU side effects scale [23] divides the side effects of psychotropic medication into 4 subgroups: psychic, neurological, autonomic, and other. Each item is classified according to severity from 0 (absent) to 3 (marked interference).

■ Statistical analysis

Once the database had been created with all the variables collected, a statistical analysis was carried out using the program package SPSS [25] version 15.0.

A chi-squared test was used to compare the qualitative variables. Their means were compared using a one-way analysis of variance (ANOVA) when the variables were non-dichotomous or Student's *t*-test when they were dichotomous. To compare the results pre- and post-intervention, a paired sample *t*-test was used with a 95% confidence interval. The data are presented as the mean ± standard deviation. A p-value less than 0.05 were taken as the threshold for statistical significance of a difference. We used Cohen's *d* to calculate the effect size. This statistic is the result of dividing the difference of the means by the square root of the mean of the two standard deviations squared.

Results

The sample consisted of 34 subjects meeting the inclusion criteria referred to above. Of these, 18 (52.9%) were men and 16 (47.1%) women. Their mean age was 40.35 years (minimum 18, maximum 62 years). Regarding their place of residence, 44.1% were at a care centre full-time, 8.8% part-time, and 47.1% at home. They were all from rural home environments.

Of the participants, 64.7% were taking some previous medication: 52.9% antipsychotics, 35.3% benzodiazepines, 17.6% antiepileptics, and 8.8% antidepressants. The mean number of these drugs was 1.59 (0-3). The mean monthly paliperidone palmitate dose they received was 116.17 (75-200) mg.

With respect to changes in the scores on the ABC scale from baseline to the visit at 6 months, there were significant ($p<0.05$) decreases in all subscales: irritability, lethargy, stereotypy, hyperactivity, and loquacity **(Table 1)**. The irritability and hyperactivity subscales presented the greatest effect sizes (1.77 and 1.59, respectively). There were no statistically significant differences in scores by sex or age group, and neither by dose of paliperidone palmitate used **(Table 2)**. There were apparent dependences on whether or not the subject had previously been being treated with some type of psycho-pharmaceutical **(Table 3)** Concomitant drug use seemed to be related to greater improvements in irritability, stereotypy, and hyperactivity (although in no case with statistical significance), but to smaller improvements in lethargy ($p=0.019$) and loquacity (also not statistically significant).

Table 1: Pre- and post-treatment evaluation of the different ABC subscales.

Subscale	Basal (mean ± SD)	Final (mean ± SD)	t-value	p-value	Effect size
I. Irritability	24.32 ± 8.56	11.09 ± 6.25	13.05	<0.001	1.77
II. Lethargy	12.65 ± 9.45	9.91 ± 7.57	4.30	<0.001	0.32
III. Stereotypy	3.88 ± 4.42	2.44 ± 3.35	5.52	<0.001	0.37
IV. Hyperactivity	21.97 ± 7.67	10.71 ± 6.39	11.00	<0.001	1.59
V. Loquacity	2.62 ± 3.43	1.62 ± 2.24	3.03	0.005	0.35

Table 2: Mean pre- and post-treatment differences (M) in the ABC subscale scores after introducing different doses of paliperidone palmitate.

Subscale		I. Irritability		II. Lethargy		III. Stereotypy		IV. Hyperactivity		V. Loquacity	
Dose	**n**	**M**	**p**	**M**	**p**	**M**	**p**	**M**	**p**	**M**	**p**
75 mg	5	-9.4		-5.8		-1.8		-7.4		-0.6	
100 mg	17	-12.8		-2.2		-1.1		-11.6		-1.1	
150 mg	10	-15.8	0.254	-1.7	0.175	-1.3	0.071	-12.6	0.463	-0.7	0.648
200 mg	2	-14.0		-4.5		-4.0		-11.0		-2.5	
Total	34	-13.2		-2.7		-1.4		-11.3		-1.0	

Table 3: Mean pre- and post-treatment differences (M) in the ABC subscale scores after introducing paliperidone palmitate, depending on the prior concomitant drug treatment.

Subscale		I. Irritability		II. Lethargy		III. Stereotypy		IV. Hyperactivity		V. Loquacity	
Concomitant drugs	**n**	**M**	**p**	**M**	**p**	**M**	**p**	**M**	**p**	**M**	**p**
Yes	26	-13.9	0.201	-1.9	**0.019**	-1.6	0.356	-11.8	0.313	-0.8	0.409
No	8	-10.9		-5.4		-1.0		-9.4		-1.5	
Yes ADs	3	-10.7	0.439	-3.0	0.899	-0.3	0.191	-11.0	0.937	-0.7	0.758
No ADs	31	-13.5		-2.7		-1.5		-11.3		-1.0	
Yes APs	22	-13.8	0.482	-2.4	0.438	-1.7	0.217	-11.2	0.961	-0.9	0.715
No APs	12	-12.2		-3.4		-1.0		-11.3		-1.2	
Yes AEs	12	-15.8	0.057	-2.8	0.911	-2.3	**0.020**	-13.2	0.174	-1.1	0.855
No AEs	22	-11.8		-2.7		-1.0		-10.2		-1.0	
Yes BZDs	18	-14.4	0.233	-1.4	**0.029**	-1.9	0.068	-12.9	0.093	-1.1	0.727
No BZDs	16	-11.9		-4.2		-0.9		-9.4		-0.9	
Nº of concomitant drugs											
0	8	-10.9	0.597	-5.4	0.093	-1.0	0.134	-9.4	0.585	-1.5	0.585
1	8	-13.0		-1.1		-0.8		-10.1		-0.3	
2	8	-14.5		-1.6		-1.5		-12.9		-0.9	
3	10	-14.3		-2.8		-2.3		-12.4		-1.3	

ABB: ADs: antidepressants; APs: antipsychotics; AEs: antiepileptics; BZDs: benzodiazepines.

With regard to the metabolic parameters, the introduction of paliperidone palmitate led to statistically significant decreases in prolactin, glucose, triglycerides, and cholesterol (Table 4). The commonest post-treatment analytical alteration detected was an elevated level of prolactin with respect to the reference values. Although these levels were lower than pre-treatment, they were still high in 20 (58.8%) of the 34 subjects (81.3% women, 38.9% men; p=0.015). The overall decrease was from 63.8 ± 47.2 (10-235) ng/ml to 49.6 ± 48.0 (7-237) ng/ml, although, by sex, it was pronounced for women but practically non-existent for men (Table 4). While it was independent of the age of the participant, it was influenced by whether or not they had been receiving treatment with many concomitant drugs (Table 5).

There were no side effects of interest according to the scores on the UKU scale, with all the items being classified as absent or light. There was only one case of amenorrhea after the introduction of the drug. This involved the absence of menstruation for more than 3 months, and hence led to the withdrawal of the treatment

Table 4: The most noteworthy analytical parameters pre- and post-introduction of paliperidone palmitate.

Blood chemistry parameter	Before paliperidone palmitate (mean ± SD)	After paliperidone palmitate (mean ± SD)	t-value	p-value
PRL (ng/ml)	63.8 ± 47.2	49.6 ± 48.0	2.81	0.011
PRL women (ng/ml)	80.13 ± 50.54	59.46 ± 51.80	*5.74	0.027
PRL men (ng/ml)	35.44 ± 17.29	36.79 ± 22.10	*1.84	0.187
Glucose (mg/dl)	97.7 ± 25.4	90.3 ± 21.9	3.41	0.002
Triglycerides (mg/dl)	149.4 ± 102.9	117.8 ± 60.4	2.71	0.012
Cholesterol (mg/dl)	191.3 ± 36.0	173.6 ± 27.8	3.52	0.001
TSH (mIU/l)	3.06 ± 2.20	2.57 ± 1.20	1.22	0.232
T4 (µg/dl)	1.06 ± 0.30	1.02 ± 0.20	0.99	0.350
Folic acid (ng/ml)	6.2 ± 3.2	6.4 ± 3.0	-0.26	0.797
Vitamin B12 (pg/ml)	463.8 ± 230.6	431.9 ± 182.7	0.77	0.456

ABB: PRL: prolactin; * F was calculated. not t.

Table 5: Changes in prolactin levels (ng/ml) after introducing paliperidone palmitate, depending on the prior concomitant drug treatment.

Concomitant drugs	PRL levels before paliperidone palmitate (mean ± SD)	PRL levels after paliperidone palmitate (mean ± SD)	Significance level
Yes	68.63 ± 48.80	50.79 ± 48.67	NS
No	39.60 ± 24.52	47.37 ± 22.39	NS
Yes APs	71.44 ± 53.06	53.37 ± 53.12	NS
No APs	46.42 ± 22.83	45.10 ± 24.03	NS
Yes AEs	79.20 ± 58.71	56.90 ± 66.16	NS
No AEs	48.47 ± 25.83	45.48 ± 19.17	NS
Previous nº of psycho-pharmaceuticals			
0	39.60 ± 24.52	47.37 ± 22.39	NS
1	38.60 ± 13.16	40.25 ± 21.50	NS
2	61.91 ± 28.12	46.12 ± 25.75	NS
3	91.55 ± 65.93	60.89 ± 71.69	0.042

ABB: PRL:prolactin; APs:antipsychotics; AEs: antiepileptics; NS: not significant.

for that specific case. There were no cases of the subject's abandoning the treatment.

CONCLUSIONS

Almost a third of persons with ID take antipsychotics, with behavioural changes being the reason for this prescription in 58% of the cases [26] to the best of our knowledge, the present study is the first report of the use of paliperidone palmitate to treat behavioural changes associated with ID. There is literature [6-8,11-13] on the use of other effective and well tolerated antipsychotics (especially risperidone). Paliperidone, whether oral or injectable, has also been used for other pathologies which present serious behavioural alterations such as autism [14,17,20] and borderline personality disorder [18].

There was a statistically significant improvement on all 5 ABC subscales. The effect sizes were greatest for irritability and hyperactivity, the two worst scoring subscales at baseline. This is concordant with the findings of Stigler [14] and Kowalski [17], although this latter study was of a single isolated clinical case. This could lead us to think that the drug of the present study is particularly effective in treating the behavioural alterations related to the aforementioned two subscales.

The only effect of differences in sex, age, or paliperidone palmitate dose was with the lowest value of this dose (75 mg) which was found to be somewhat less effective in improving irritability and hyperactivity.

An excess of medication could be negative in that it might lead to greater lethargy and social withdrawal (isolation, inactivity, apathy, etc.) as reflected in the findings that prior concomitant drug treatment (total, and benzodiazepines in particular) negatively affected the subjects' improvement on this subscale after the introduction of paliperidone palmitate (Table 3). The fact of having some previously prescribed medication, especially antipsychotics,

antiepileptics, and benzodiazepines, led to greater improvement in irritability, stereotypy, and hyperactivity, but less improvement in lethargy and loquacity. Similarly, the greater the number of concomitant psychotropic drugs taken, the greater the improvement in irritability, stereotypy, and hyperactivity, and the less in lethargy and loquacity, although none of these differences were statistically significant. This suggests that persons with ID and severe behavioural alterations often need polymedication to reduce their hyperactivity and irritability which are the most worrisome aspects for those living with them. Nevertheless, such polymedication might be negative, or at least not so positive, for other aspects of their lives.

In other studies of similar populations, it was usual for the participants to have already been taking concomitant drugs. An example is the study of Frighi [7] in which the average use was 2 drugs per participant, with risperidone being that most used. The number in the present study was similar but slightly lower. The fact of the low hepatic metabolism of paliperidone palmitate [16] and the advantage of its monthly administration would seem to favour its use in groups of polymedicated participants such as those with ID, since it would reduce drug interactions and improve therapeutic compliance.

The monthly dose of 116.17 mg used in our study was higher than the 103 mg used for a population of 78 psychotic participants in the same health area and time period [27]. This may indicate that higher doses of this drug are needed to control behavioural changes than psychotic symptoms.

Almost half of persons with ID and behavioural disorders suffer metabolic syndrome, with the use of antipsychotics being one of the main causes [28]. Our use of paliperidone palmitate was safe and well tolerated, improving most metabolic parameters, and there was only one case of treatment withdrawal due to a side effect (amenorrhea). No other adverse effects of interest were recorded.

The hyperprolactinemia that occurred in more than 50% of the participants was consistent with the observations reported in other similar studies. For example, in a study of 138 persons with ID who were taking antipsychotics, Frighi et al. [7] reported that 44% of the men had hyperprolactinemia and 47% of the women (45% including both sexes). The proportions presenting hyperprolactinemia in this study were as follows: of the 66 subjects who were taking risperidone, 70% of the men and 72% of the women; of those taking amisulpride, 100% of both the men and the women; and of those taking other antipsychotics, 7% of the men and 9% of the women. Hence, in our study as in similar ones [14], raised prolactin levels were severer in women than in men. This difference could be due to the relative difference in estrogen levels between men and women and the role of estrogen in stimulating prolactin synthesis [29].

The present study had various limitations. One is the fact that most of the participants had some previous concomitant medication that might have masked the actual effect of paliperidone palmitate, even though that previous treatment had been ineffective and had undergone slight modifications when the study drug was added. With regard to the measurement instrument, it is necessary to bear in mind that it is a scale which involves subjective assessment of different dimensions of behaviour. Another limitation is the moderately small number of participants and the non-random, consecutive selection procedure. Neither was there a control group with which to compare the results. This meant that the same individuals on whom the intervention was performed acted as the controls (repeated measures) – a less effective design in searching for evidence than other designs with independent control groups. This is why other randomised double-blind studies with control groups will be needed to correctly establish the efficacy and tolerability of paliperidone palmitate for this population.

Conflict of Interests

The authors declare that they have no conflicts of interest.

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