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Long-acting injectable risperidone in treatment resistant borderline personality disorder. A small series report

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Introduction. Borderline personality disorder (BDP) is usually treated with a combination of antipsychotic and anticonvulsant drugs although only limited efficacy is obtained in many patients. A major problem in the treatment of BPD is the lack of compliance derived form the pathological impulsivity of BPD patients.

Methods. Twelve severe BPD patients refractory to previous treatment with drug combinations for three months were treated with intramuscular long-acting risperidone for a six-month period. Clinical changes were rated with the Clinical Global Impression (CGI), the Brief Psychiatric Rating Scale, anxiety and aggression scales. Functional improvement was evaluated with the Global Assessment of Functionng (GAF).

Results. Six-month treatment with IM risperidone was associated with significant improvement of CGI (t: 5.7; gl: 10; $p < 0.01$) and of GAF (t: –4.5; gl: 10; $p < 0.01$). Clinical improvement was robust after the first month of treatment. No relevant extrapiramidal side effects were reported with the exception of mild psychomotor slowing which requires dose adjustments in four patients.

Conclusions. Treatment with i.m. long acting risperidone during six months was associated with significant clinical and functional improvement and excellent tolerability in a group of BPD patients refractory to previous treatment. The results indicate that the effect of IM risperidone in BPD should be further investigated in large placebo-controlled trials.

Key words:
Risperidone. Borderline personality disorder.

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Risperidona intramuscular de acción prolongada en el trastorno límite de la personalidad resistente al tratamiento. Un estudio piloto

Introducción. El uso de fármacos antipsicóticos de segunda generación en combinación con fármacos anticomiciales en el trastorno límite de la personalidad (TLP) es común, pero muchos pacientes obtienen con ellos una mejoría muy limitada. Uno de los inconvenientes principales del tratamiento es el deficiente cumplimiento debido a la propia psicopatología impulsiva de los pacientes con TLP.

Métodos. Doce pacientes con TLP grave y refractarios a tratamientos de combinación previos durante 3 meses fueron tratados con risperidona intramuscular de acción prolongada por un período de 6 meses. Se evaluaron los cambios clínicos mediante la Impresión Clínica Global (CGI), la *Brief Psychiatric Rating Scale*, las escalas de ansiedad y de depresión de Hamilton y la escalas de agresión. Se evaluó la mejoría funcional mediante la evolución de la Escala de Funcionamiento Global (GAF) del DSM-IV.

Resultados. El tratamiento durante 6 meses se asoció a una mejoría significativa reflejada en la CGI (t: 5,7; gl: 10; $p < 0,01$) y en la GAF (t: –4,5; gl: 10; $p < 0,01$) que comenzó a consolidarse a partir del primer mes de tratamiento. No se registraron efectos extrapiramidales relevantes, con excepción de un moderado enlentecimiento psicomotor que requirió ajustes de dosis en cuatro pacientes.

Conclusiones. El uso de risperidona intramuscular de larga duración durante 6 meses se asoció a una significativa mejoría clínica y funcional y a una excelente tolerancia en un grupo de pacientes con TLP resistentes a tratamientos previos, lo que sugiere la conveniencia de investigar este efecto en ensayos clínicos controlados.

Palabras clave:
Risperidona. Trastorno límite de la personalidad.

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INTRODUCTION

Patients with intense emotional instability and impulsive behaviors that cause severe functional impairment are included under the category of borderline personality disorders (BPD). However, patients may differ greatly in their clinical characteristics and in the severity of the disorder. In recent years, a number of clinical trials, some of them placebo-controlled, have been published with antipsychotic drugs such as olanzapine[1-3], risperidone[4] or ziprasidone[5], and with anticonvulsant drugs such as valproate[6], topiramate[7], oxcarbazepine[8] or lamotrigine[9]. However, patients with borderline personality disorder are still treated on the bases of shared clinical experience and there is still no drug having a specific indication for the disorder.

In general, the clinical trials that have been published are of short duration and it is very difficult to extrapolate the information offered to long-term clinical experience with BPD patients. In addition to this, severe BPD patients cannot be included in controlled clinical trials so that a bias may be produced towards less severe patients in the selection of the study sample.

One of the main problems in the treatment of BPD patients is patient compliance with the therapeutic guidelines. Although this can be applied to all patients with mental disorders, the emotional instability and behavioral impulsivity of BPD patients make them especially prone to not comply with the treatment. This frequently leads to a sporadic and abusive use of the medication[10]. In this sense, using injectable and long-acting medications may be a way to improve therapeutic compliance. That is why this preliminary study with long-acting injectable risperidone was designed in patients with borderline personality disorders that are especially severe and refractory to other treatments.

METHODS

Twelve outpatients from the Personality Disorder Unit diagnosed of Borderline Personality Disorder refractory to previous treatment were enrolled in the study. Every case was diagnosed by a psychiatrist expert in these pictures and with the SCID-II structured interview for personality disorders[11].

Inclusion criteria were the following: *a)* having marked severity defined by a score of more than 16 point on the Zanarini scale for BPD[12] and a score greater than or equal to 5 points (extremely severe disease) on the Clinical Global Impression Scale (CGI). In practice, these scores mean pictures: *a)* having high emotional arousal, with psychomotor agitation and uncontrolled behaviors; *b)* patients in whom no substantial improvement was observed after previous protocolized treatment of at least three months. No age or gender criteria were applied.

Exclusion criteria were the following: *a)* lifetime history of schizophrenic or schizophreniform disorder or bipolar disorder; *b)* psychosis due to substance use disorder; *c)* current severe major depressive disorder; *d)* serious medical complications or pregnancy and *e)* known intolerability to risperidone or to intramuscular injections.

The patients were selected consecutively when they were in this clinical condition (table 1) and gave their written consent for the study. The enrolment period was one year.

The previous treatment was by protocol and consisted of a combination of drugs that were progressively added when there was lack of response. This combination began with an antidepressant drug (venlafaxin or duloxetine), plus an antipsychotic drug (olanzapine, ziprasidone or quetiapine) and an anticonvulsant drug (oxcarbazepine or topiramate). All these were used in progressive doses until the maximum permitted dose or maximum tolerated dose for the patient were reached. Benzodiazepine drugs were being used at doses equivalent to 60 mg of diazepam daily in all of the patients enrolled in the study since they were especially serious and refractory to treatment.

In addition to the structured interview, the Hamilton anxiety[13] and depression[14], Brief Psychiatric Rating Scale (BPRS)[15] and Overt Aggression Scale (OAS)[16] were applied. As efficacy measurements, the modifications of these scales in the Clinical Global Impression (CGI) scale as well as the changes in the global assessment of functioning (GAF) scale of the DSM-IV were used. Adverse effects were reported by the patients and investigated by the clinician from a side-effects list.

Treatment was initiated with an intramuscular injection of 37.5 mg of long-acting risperidone repeated every two

Table 1 Characteristics of the sample

Age	Gender	Zanarini score	HAM anxiety score	CGI	Evolution time
34	Male	17	34	5	10
25	Male	18	32	5	7
30	Female	20	21	6	14
33	Male	18	38	6	15
27	Female	22	20	6	5
34	Female	19	20	5	4
26	Female	18	31	5	5
25	Male	21	34	6	7
22	Male	22	24	6	4
34	Male	17	30	5	9
44	Female	24	23	5	7
26	Female	18	30	5	7

weeks while reducing the benzodiazepine by 25% each week. The antipsychotic drug that the patients were being treated with previously was withdrawn during the first week of treatment with IM risperidone, reducing the dose by 25% every two days.

The IM risperidone dose was increased to 50 mgs if sufficient therapeutic response was not achieved in one month. In the same way, if the patient suffered difficult-to-tolerate side effects, the dose was reduced to 25 mgs. When required due to the clinical conditions, the benzodiazepine dose was reinitiated for as long as necessary. The rest of the previous treatment was not modified during the study. Study duration was six months, after which risperidone was withdrawn.

Clinical evaluations were conducted every week during the first month of treatment and monthly until the end of the study. Side effects were investigated at each evaluation.

The data were studied using descriptive analysis of the results and making a statistical study of the clinical changes during the study, performed with the SPSS statistical program, version 12.

RESULTS

During one year, 12 out of a total of 35 patients complied with the inclusion criteria and were treated with im risperidone.

After six months of treatment, a statistically significant change towards improvement was observed in both the CGI and GAF (global assessment of functioning scale) (table 2) (CGI: t: 5.7; df: 10; $p < 0.01$) (GAF: t: –4.5; df: 10; $p < 0.01$). Improvement in the CGI and GAF can be observed after the first month of treatment and is statistically significant in the third month. At three months of treatment, 7 out of the 12 patients (58.3%) had CGI of change equal to 1 or 2, so that they were considered to be responders to treatment. The number of responders increased to 8 (66%) in the sixth month.

The treatment led to a significant reduction in the scores for anxiety, aggressivity, and hostility scales and on the Global scale of intensity of the borderline syndrome (Zanarini Scale) (table 2).

Only 1 out of the 12 patients abandoned the treatment due to symptoms of stiffness and intolerable akathisia. The rest had mild adverse effects. The most frequent of these were psychomotor slowing and akathisia (table 3). No patient suffered stiffness, dystonias or other clinically important extrapyramidal symptoms. The dose had to be reduced in 6 of the patients from 50 to 37.5 mg due to psychomotor slowing or sedation that caused serious functional limitation. Biperiden was used in 3 patients to correct akathisia.

Mean dose used was 42.4 mg every two weeks (range 37.5-50). Maximum dose reached was 50 mgs in 9 patients, and had to be reduced to 37.5 mg due to adverse effects in 6 of them.

Table 2 Measurements of efficacy

	Initial	1 month	3 months	6 months
Clinical global impression	5.4, 0.5	4.2, 0.8*	3.4, 0.6**	3.2, 1.0**
GAF	55.4, 4.9	59.6, 5.3	64.1, 7.2**	70.9, 9.9**
HAM-anxiety	24.1, 3.5	21.1, 3.9	19.2, 5.3*	17.5, 5.1**
Aggression (OAS)	13.1, 6.3	7.6, 5.4**	5.6, 2.9**	5.1, 2.6**
Hostility (BPRS)	3.5, 1.6	2.4, 1.3**	2.0, 1.1**	1.8, 1.0**

Statistical significance of the comparison with the values at onset of treatment. *$p<0.05$; **$p>0.01$.

DISCUSSION

The results of this small study are indicative that the use of risperidone may be efficient in patients with severe personality disorder resistant to other treatments. Risperidone produces a significant reduction of symptoms of anxiety, agitation, behavioral lack of control and emotional instability, thus permitting considerable functional improvement of the patients. The effect of long-acting risperidone is not translated into a sedative effect or psychomotor blockage of the patients except in those cases in which the doses were excessive and had to be reduced.

The therapeutic action of antipsychotic drugs in borderline personality disorders has been described in some recent studies. Some of these studies have been placebo-controlled, including those with olanzapine[1,3] and aripiprazole[17], while others have been open-label studies with risperidone[4] or quetiapine[18]. The duration of most of these studies was short, evaluating the therapeutic effect in a period of 8 to

Table 3 Distribution of side effects

N = 12 patients	Mild	Moderate	Serious	No
Psychomotor slowing	7	1		4
Akathisia	7	1		4
Sedation	3			9
Stiffness	2			10
Other adverse effects	3			9

12 weeks. In general, studies with antipsychotics suggest that the their therapeutic effect is due to an overall improvement of the patient's affective and cognitive aspects and that this is independent of the presence or absence of accompanying psychotic symptoms or paranoid traits[2,3]. The only studies published with injectable antipsychotics in borderline personality disorder consisted in acute treatment of agitation in the emergency wards[5,19] where it seems to produce a beneficial reduction of the emotional symptoms and behavioral lack of control.

There are different reasons why IM risperidone has been effective in patients in whom other drug combinations had not worked. Howeves, these cannot be verified with the current data. One possible explanation could be found in the guarantee of therapeutic compliance offered by the use of IM risperidone. Another explanation attributes the efficacy to the pharmocokinetic properties of the intramuscular form, that achieves more stable sufficient concentrations than the oral forms of treatment[20,21].

The drug was very safe in its use and considerably tolerable. There were no severe adverse effects and the extrapyramidal symptoms were generally limited to a moderate and correctable akathisias with anticholinergic drugs and a mild psychomotor slowing that sometimes made it necessary to partially reduce the dose. Weight changes were not significant although this information is difficult to evaluate since the patients had previously received other antipsychotics that may have caused weight gain.

The results of this study suggest that risperidone may have a long-term beneficial effect, allowing for progressive improvement of the patient in his/her interpersonal and social functions since most of the patients treated return to different psychosocial activities. The risk of shifting from the emotional and behavioral state of lack of control to states of apathy, abulia or emotional blunting secondary to treatment with dopamine antagonists should be considered in these patients, although these effects did not appear in the study. This favorable profile of side effects of long-acting intramuscular risperidone has been previously described in trials conducted in patients with schizophrenia[20] and bipolar disorder[22]. It should be stressed that all the patients of the study received psychosocial support that favored motivation and their activity in addition to the drug treatment. It could be considered if the use of intramuscular risperidone in patients who do not receive any other type of psychosocial supports would also be risk free for apathy and lack of motivation.

The doses used were calculated by extrapolating the oral doses of risperidone used previously in these disorders, that generally correspond to approximately half of the doses used in the patients with schizophrenia[4,21].

In a study with such a small sample as this one, it is not possible to state if the beneficial effects are mainly due to the reduction of anxiety, excitability or other symptomatic components. Patients with predominance of symptoms of anxiety experienced subjective sensation of greater calmness and patients with reactive emotional lack of control reported a sensation of less irritation. In successive studies with larger samples, the changes in the domains of anxiety, hostility, mood state, impulsivity and social adjustment could be evaluated in the long term separately, thus being able to obtain greater information on the nature of the drug effect. In view of the clinical heterogeneity of the patients who may be diagnosed of BPD, the definition of the specific therapeutic pattern of the drug may be of interest to rationalize its use in the best way.

CONCLUSIONS

The use of long-acting injectable risperidone in a series of patients with serious borderline personality disorder refractory to previous treatments demonstrated to be safe and tolerable, producing a significant clinical improvement without psychomotor inhibition for the patients. The prolonged use of up to six months of treatment was accompanied by progressive improvement in interpersonal and sociolaboral adjustments and made it possible to obtain considerable gain in independence for the patients.

The main limitations of the study are its reduced sample size and its open-label and non-controlled nature that should be addressed in future clinical trials. However, these preliminary data constitute a sufficient sign that the use of long-duration injectable risperidone could be effective in the long-term treatment of BPD and justify the conduction of trials on a larger scale.

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