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Neuropsychological effects of maintenance treatment with Clozapine in Treatment-Resistant Psychotic Disorder

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Introduction. Clozapine is a second-generation antipsychotic drug that is mainly prescribed for treatment-resistant psychotic disorder. It is known to have several undesirable side effects, including cognitive functional complaints, such as memory or attention. The aim of this work is to study if reduction of the dosage within the therapeutic margins could improve cognitive performance of Clozapine treated patients. To do so, a study was made of the relationship between Clozapine plasma levels and neuropsychological performance in patients undergoing Clozapine monotherapy.

Material and Methods. This is a single-blind design study of the correlation between Clozapine plasma levels and neuropsychological testing in a sample of 19 patients with treatment-resistant psychotic disorder in whom Clozapine was the only psychotropic drug. Spearman correlations were carried out between neuropsychological variables and Clozapine plasma levels. Additionally, the sample was divided into two groups between patients with high Clozapine plasma drug levels (Clz pl \geq 300 μ g/L) and low ones (Clz pl<300 μ g/L). MANOVA was performed to determine neuropsychological differences between the two groups. Subsequently, a linear regression model was carried out to predict neuropsychological performance.

Results. There was no significant Spearman correlation between neuropsychological scores and Clozapine plasma levels ($p>0.1$). MANOVA showed no significant differences between the two groups in any of the tests administered, although there was a trend towards significance in the number on attempts of the Card Sorting Test (WCST), where subjects with high levels of Clozapine showed worse

performance ($F=3.86$; $df=1.17$; $p=0.07$). The linear regression model showed that only plasma levels significantly predicted executive performance, explaining 31% of the variance ($F=3.62$; $df=2.16$; $p=0.05$).

Conclusion. No relationship between plasma levels of Clozapine and cognitive performance has been found. This result suggests that it is not desirable to reduce a relevant dose of Clozapine in patients with cognitive complaints.

Key words: Resistant Psychotic Disorder, Clozapine, Neuropsychological performance, Executive functions

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Efectos neuropsicológicos del tratamiento de mantenimiento con Clozapina en el Trastorno Psicótico Resistente

Introducción. La Clozapina es un antipsicótico de segunda generación, indicado en casos de trastorno psicótico resistente al tratamiento convencional. Presenta varios efectos secundarios, entre ellos, las quejas sobre la función cognitiva como la memoria o la atención. El objetivo es estudiar si la reducción de la dosis dentro de los márgenes terapéuticos podría mejorar el rendimiento cognitivo de los pacientes tratados con clozapina. Para ello se estudia la relación entre la concentración plasmática de Clozapina y el rendimiento cognitivo en pacientes en monoterapia con Clozapina.

Material y Métodos. El estudio es un diseño simple-ciego de correlación entre niveles plasmáticos de Clozapina y rendimiento neuropsicológico en una muestra de 19 pacientes con trastorno psicótico resistente en monoterapia con Clozapina. Se realizaron correlaciones de Spearman entre variables neuropsicológicas y niveles plasmáticos. Adicionalmente, la muestra se dividió entre pacientes con niveles plasmáticos altos (Clz pl \geq 300 μ g/L) y bajos (Clz pl<300 μ g/L) de Clozapina. Se llevó a cabo una MANOVA para determinar

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diferencias entre grupos. Se realizó un análisis de regresión lineal para predecir el rendimiento neuropsicológico.

Resultados. No se halló ninguna correlación significativa entre las pruebas neuropsicológicas y los niveles plasmáticos de Clozapina ($p>0.1$). La MANOVA no mostró diferencias significativas entre los dos grupos en ninguna de las pruebas administradas, aunque sí se observó una tendencia a la significación en los análisis univariantes donde en el número de intentos del Test de Clasificación de Tarjetas (WCST) los sujetos con niveles altos de Clozapina mostraron un peor rendimiento ($F=3.86$; $gl=1.17$; $p=0.07$). El modelo de regresión lineal mostró que el único factor significativo fueron los niveles plasmáticos, explicando un 31% de la varianza ($F=3.62$; $gl=2.16$; $p=0.05$).

Conclusiones. No se evidencia relación entre los niveles plasmáticos de Clozapina y el rendimiento cognitivo. Este resultado sugiere que no es conveniente reducir de forma relevante la dosis de Clozapina en pacientes que se quejan de disfunciones cognitivas.

Palabras clave: Trastorno Psicótico Resistente, Clozapina, Rendimiento neuropsicológico, Funciones ejecutivas

INTRODUCTION

Schizophrenia is undoubtedly the group of most complex disorders affecting the human being. It has a lifetime prevalence that ranges slightly below 1%, causing a first magnitude health care problem. Clinically, it is characterized by involvement of all the areas involved in the area of relationships in life such as perception, ideation, effectiveness, and cognitive function.

Even though the introduction of antipsychotic drugs positively modifies the course of this disease, it is estimated that 20 to 50% of patients are resistant and have insufficient therapeutic response.^{1,2}

Clozapine is a drug that has been indicated in the cases of schizophrenia that are resistant to conventional treatment since 1988 when Kane demonstrated its efficacy in this population of patients.³ Several authors have defined this resistance as absence of clinical response to more than one antipsychotic administered in adequate dosage and time.^{3,4} Treatment resistant criteria are defined based on: 1) evidence of adequate treatments (a minimum of 3 trials of 6 weeks in the last 5 years with at least two typical antipsychotics of different chemical classes, in equivalent doses of at least 1g/day of Chlorpromazine) without significant relief of the symptoms, b) persistence of positive psychotic symptoms with moderate to elevated score on at least two of the four items of positive symptoms on the Brief Psychiatric Rating Scale (BPRS), c) presence of moderate or severe disease, defined as a minimum of 45 points on the BPRS and a "moderate" or superior score on the Global Impression Scale

and d) non-existence of a period of good social or laboral adjustment in the last 5 years.

In 1984, Clozapine was withdrawn from the market because of the risk of agranulocytosis observed in the Finnish population. Some healthcare sites have continued to use it on a "compassionate use" basis and have observed frank clinical improvements in up to 60% of the patients resistant to other drugs.⁵

In 1988, the above-mentioned study of Kane et al. was published. This study demonstrated the efficacy of clozapine in conventional antipsychotic resistant subjects³ and the use of this drug rapidly became generalized in this subpopulation of patients.

On the other hand, the superiority of clozapine in resistant patients has also been observed in relationship to second-generation antipsychotic drugs. The results of the second phase of the pragmatic study CATIE are especially relevant.⁶ The patients from the first phase who had discontinued the drug and were considered resistant to the tested therapeutic option were randomized to take Clozapine or another second-generation antipsychotic drug other than that which they had received in phase 1. The results have shown a highly significant superiority of Clozapine in relationship to the other antipsychotics studied (olanzapine, quetiapine and risperidone). These data suggest that Clozapine may be the first therapeutic option in psychotic patients resistant to a single test with any antipsychotic drug, whether 1st or 2nd generation.

Reintroduction of Clozapine stimulated the development of other drugs having atypical pharmacodynamic profile, constituting the second generation of antipsychotics.

However, some side effects of Clozapine are reason for concern since they may condition therapeutic compliance in a group with few other therapeutic options. Within the factors that lead to the withdrawal or decrease of the drug dose are, among others, complaints regarding cognitive performance. It is well known that psychotic disorders per se affect neurocognition, especially attention, executive functions, verbal fluency and memory.⁷

Previous studies that have investigated the relationship between Clozapine and cognitive deficit in patients with psychotic disorder have found contradictory results. Some groups indicate improvement of attention, executive functions, verbal fluency and memory with said antipsychotics.⁸ In this aspect, it has been proposed that Clozapine would increase dopamine release in prefrontal areas through its partial agonism on the 5-HT_{1A} receptors. This pharmacodynamic property could contribute to its action regarding cognitive symptoms of schizophrenia.^{9,10} On the other hand, the action of its main metabolite, N-desmethylozapine (NDMC), as positive allosteric

modulation of the M1 and M4 receptors on the hippocampal level suggested in preclinical studies, could also explain its properties on the cognitive function through the modification of the cholinergic activity.¹¹

Thus, improvement in cognition could be partially due to the clinical stabilization achieved in this type of patient, whose history of poor response to other drugs have entailed poor evolution of the psychotic disorder with consequent greater cognitive dysfunction. In addition to the sedative effect induced by the blockade of the H₁¹² receptors, Clozapine would act by antagonizing the muscarinic receptors, negatively affecting the cognitive function.¹³

Decreasing the dose or elimination of Clozapine may put the clinical stability of these patients at risk.¹⁴ The decision to make changes in the drug dosage should be based on evidence of the utility and safety of these changes and not only on the subjective complaints of the patient regarding their cognitive performance.

This study has aimed to determine if there is a relationship between plasma levels of Clozapine and cognitive function in chronic psychotic patients treated with therapeutic doses of Clozapine. If this relationship is confirmed, moderate reduction of the dose would be reasonable. If, on the contrary, no correlation is found between these two variables, the reduction of the dose would imply a not very useful and difficult to assume risk.

MATERIAL AND METHODS

This is a simple blind designed study of correlation between plasma levels of Clozapine and neuropsychological performance in patients with resistant psychotic disorder treated in monotherapy with Clozapine. The patients were enrolled from the outpatient clinics of the Psychiatry Department of the Hospital of Sant Pau in Barcelona.

This site attends to patients who are admitted to the acute unit of the site and patients with resistance to different treatments and of difficult management referred from Mental Health Centers (specialized primary care) from the area of influence (somewhat less than half a million inhabitants). Nineteen (11 men and 8 women) out of the 106 patients treated with Clozapine who fulfilled the following inclusion criteria were included in the study: those diagnosed of Schizophrenic Disorder or resistant Schizoaffective disorder (DSM-IVTR¹⁶), who were receiving treatment with Clozapine for at least 5 years, who remained in monotherapy with this drug, and who were clinically stable during this period (e.g., with a score under 21 in the Brief Psychiatric Rating Scale, BPRS).¹⁵ Exclusion criteria were presence of concomitant neurodegenerative diseases and receiving treatment with other antipsychotic drugs, mood stabilizing drugs or antidepressants in order to prevent

the possible cognitive dysfunction from being attributed to the combined use with other psychotropic drugs. Thirty-six of the remaining patients of the initial sample were ruled out due to exacerbation of positive symptoms during the last 5 years, 12 because of additional treatment with lithium, 16 due to treatment associated to antidepressants and 23 because they had initiated a combination with the second antipsychotic.

In addition, the sample was divided by plasma levels into high (Clz pl \geq 300 μ g/L) and low (Clz pl<300 μ g/L)¹⁷ to compare the groups having greater or lesser risk, respectively, of possible cognitive affectation.

The clinical evaluation tools used were Mini Mental State Evaluation (MMSE)¹⁸ for screening of cognitive deterioration and BPRS to measure clinical stability. Cognitive evaluation included the Ray learning Test (AVLT)¹⁹ to evaluate verbal memory, the WAIS-III Digits Test²⁰ for attention and the Card Sorting Test (WCST)²¹ and Phonetic Verbal Fluency Test (PMR)²² to evaluate executive function. These tests were administered by two trained psychologists who were blinded in regards to the pharmacokinetic variable and group assignment. All the evaluations were performed in the afternoon to minimize the sedative effect produced by the drug because all the patients received them as a single nighttime dose.

Blood was drawn between 8 a.m. and 10 a.m. to determine Clozapine plasma levels (Clz pl). The HPL-C technique was used to measure drug plasma levels, whose therapeutic range is between 200-600 μ g/L.

The data were analyzed using the SPSS statistical program (v.18). Analysis of the clinical and demographic data was performed with the T- and Chi-square tests for quantitative and qualitative variables, respectively. Spearman's correlations between the neuropsychological variables and Clozapine plasma levels were performed for the principal hypothesis. A multivariate variance analysis (MANOVA) was also performed to compare the means of the neuropsychological tests between the high level and low level groups of Clozapine. Finally, a linear regression analysis was made to determine neuropsychological performance based on Clozapine plasma levels and other clinical variables.

RESULTS

All the patients enrolled were clinically stable and had a global mean score of 11.9 points on the BPRS. Spearman's correlations did not show any significant relation between the scores on the neuropsychological tests and the Clozapine plasma levels (see Table 2).

The sample was finally divided into two groups to analyze the comparison of means: one made up of 10

Table 1 Descriptive variables of the two study groups

	Low levels of Clz pl (n=9)	High levels of Clz pl (n=10)	F/t/x ²
Age (years)	45 (10.3)	47.2 (7.5)	0.300
Gender (M/W)	5/4	6/4	0.040
Education (years)	13.1(3.2)	11.4(2.4)	1.800
Laterality (R/L)	9/0	9/1	1.300
DSM-IVTR Diagnosis (CPS/SAD)	6/3	9/1	1.600
BPRS	12(8.2)	11.8 (7.4)	0.003

M: man; W: woman; R: right; L: left; CPS: Chronic Paranoid Schizophrenia; SAD: Schizoaffective Disorder. No significant differences were found between both groups.

Table 2 Spearman's Correlation between the neuropsychological variables and plasma levels of Clozapine

	Spearman's r	Significance (p)
Verbal Memory - RAVLT		
Total Learning	-0.15	0.5
Delayed Recall	0.01	0.9
Rate of Forgetting*	-0.17	0.5
Attention-Digits	0.21	0.4
Verbal Fluency - PMR	-0.03	0.9
Executive Function -WCST		
No. of Categories	-0.23	0.4
No. of Attempts	0.39	0.1
No. of Perseverative Errors	0.35	0.1

*Rate of forgetting: difference in % between total recall and delayed recall.

patients with high Clozapine plasma levels (Clz pl \geq 300 μ g/L) and a second group made up of 9 patients with low levels (Clz pl<300 μ g/L). Demographic and clinical data of both groups are detailed in Table 1. Significant differences are not seen between them.

The results of the MANOVA did not show significant differences between the two study groups in any of the neuropsychological tests administered (see Table 2). However, a tendency to significance in the univariate contrast of the number of attempts on the WCST where the subjects with high levels of Clozapine showed worse performance on the executive test ($F=3.86$; $gl=1.17$; $p=0.07$) was observed. The predictor variables included in the linear regression model were plasma levels, psychopathological severity, patient age and educational level. Performance on the number of attempts in the WCST test was defined as dependent variable. Finally, the linear regression model significantly predicted performance on the WCST test ($F=3.62$; $gl=2.16$; $p=0.05$), 31% of the variance in the results of the test of number of attempts on the WCST being

explained by the Clozapine levels. The two variables included in the model were plasma levels and score on the BPRS, although only the former had a significant weight in the model ($\beta=0.5$; $p=0.03$).

DISCUSSION

The results from the present study have shown that the neuropsychological performance of patients being treated with Clozapine was not correlated with the plasma levels of the drug therapeutic dose ranges. It also did not vary significantly based on whether the plasma levels were high or low, except for the tendency observed in the categorization test in which the patients with high plasma levels had worse performance. This result was confirmed with the regression model in which 30% of performance was accounted for by the drug plasma levels in the executive test alone. In the remaining cognitive functions, no differences were found that could be attributable to the plasma levels of Clozapine, including the PMR test for measuring verbal fluency, which together with a number of attempts of the WCST, is also included among the executive function tests.

Therefore, the possible cognitive dysfunctions of the patients treated with Clozapine would not be sufficient reason to run the risk of relapse associated to a decrease in dosage since reductions of the plasma levels within the therapeutic range²³ would not imply a significant improvement of the cognitive function. These results also suggest that individual tolerability more than a generalizable pharmacokinetic factor is the most important factor in cognitive dysfunctions arising during treatment with Clozapine.

The results of this study would suggest that drug dose should not be decreased when faced with possible complaints by the patients regarding cognitive function. Only 31% of the "executive performance" out of all of the neuropsychological tests administered could be attributed to plasma levels of it. Furthermore, there were no differences

Table 3 Results of the neuropsychological tests administered in the two study groups

	Low levels of Clozapine (n=9)	High levels of Clozapine (n=10)	F	p
Memory				
Total learning	38 (11.96)	33.5 (10.01)	0.796	0.4
Delayed recall	7.88 (3.4)	7.8 (3.2)	0.003	0.9
Rate of Forgetting	23.79 (21.1)	17.65 (14.9)	0.550	0.5
Working Memory				
Direct Digits	8.2 (1.85)	8.9 (1.6)	0.700	0.4
Inverse Digits	5.6 (1.3)	5.5 (1.43)	0.069	0.8
Phonetic Fluency				
P	16.55 (4.3)	14.1 (5.2)	1.250	0.3
M	13.5 (3.2)	10.6 (4.9)	2.300	0.2
R	10.88 (2.97)	11 (4.1)	0.005	0.9
Executive Function (WCST)				
No. of Attempts	114.8 (20.7)	127.7 (0.9)	3.859	0.07
No. of Perseverative Errors	69.6 (13.9)	68 (11)	0.085	0.8
No. of Categories	3.1 (2.4)	1.9 (1.7)	1.650	0.2

between the high and low level groups of Clozapine in regards to any of the neuropsychological tests. Therefore, these results together with the findings of other studies that have observed that there is a risk of clinical relapse when Clozapine dose is decreased or withdrawn indicate that the complaints on cognitive function should not be sufficient reason to modify the drug doses. On the other hand, sleep hygiene measurements, physical activation or moderate use of caffeine could be suggested as measures that could relieve the sensation that the patient has of feeling they are not sufficiently "awake" or alert when their daily life requires a certain cognitive performance is required.

Furthermore, it can be stressed that no significant differences were observed for "attention" regarding high and low plasma levels. This is indicative that the cognitive functioning of these patients would not be mediated by the sedative effects induced by the antihistaminic activity of Clozapine.

One of the limitations of this study is that there was no control group in the neuropsychological study. This means a limitation for the generalization of the results, although the neuropsychological evaluations were always blind in relationship to the Clozapine plasma levels. Furthermore, variables related with the disease such as years of evolution or number of previous hospital admissions were not taken into account. In future studies, this sample should be extended and a control group obtained. In addition, a prospective follow-up of the neuropsychological perfor-

mance in patients who initiate treatment with Clozapine should be conducted. This would make it possible to observe the effect of the initiation and maintenance of the drug on cognitive function.

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