Electroconvulsive therapy and psychotropic concomitant treatment: study of clozapine and mood stabilizers

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Poster number: P.2.h.011

Introduction

Based on an erroneous belief in a biological antagonism between schizophrenia and epilepsy, in 1934 Meduna used pharmacological methods to induce seizure activity for treating patients with schizophrenia. He began with intramuscular injections of camphor and later he switched to Metrazol. In 1938, the Italian scientists Cerletti and Bini defined the parameters necessary for applying electricity directly to the human scalp. (1) This was the beginning of electroconvulsive therapy (ECT). Because of its success in treating acute schizophrenia, ECT has been also tried in patients with other psychiatric diseases. Nowadays ECT indications are mood disorders, essentially severe depression and acute mania, drug-resistance schizophrenia, schizoaffective disorders and catatonic syndromes. Besides, ECT has been found to have neurobiological effects that may help in the treatment of certain medical conditions in patients who have been refractory to or intolerant of other therapies. (1) Regarding the serious clinical condition of patients treated with ECT, it is not uncommon that they are under psychotropic treatment. It is known that several drugs can affect the electrical parameters of ECT, including seizure duration which is a determining factor of ECT effectiveness. (2) Although the potential impact of pharmacotherapy on ECT is still up-to-date, there is limited literature regarding this issue. Guidelines suggest to reduce doses or discontinue the treatment before start ECT.(3) (2) However, many authors consider that there is not enough evidence that ECT and mood stabilizers could not be used at the same time. Clinicians tend to proceed using an individual point of view. As for antipsychotic treatment, clozapine is the most controversial. However the confirmed beneficial effects of combined therapy, the adverse events on electrical parameters have prevented physicians from prescribing it. (4) (5)

Aims

The aim of this study is to provide further information about the effects of some psychiatric drugs upon ECT efficacy. We consider the following hypotheses:

- Clozapine prolonged the duration of ECT induced seizures
- Antiepileptic mood stabilizers clinically significant increase stimulus parameters

Methods

We obtain our sample from a cohort of patients receiving ECT in our psychiatric unit care. The treatment was decided by clinical indication and the cohort included both inpatient and outpatient. No differences between acute and maintenance ECT treatment were taken into account. The sample contained all ECT sessions received for each patient. We selected only the patients taking concomitant treatment, either with clozapine or anticonvulsive drugs prescribed as a mood stabilizers. We performed an observational, case-control study for contrasting the conditions listed above. In the first place, we studied the convulsion duration regarding the presence of concomitant treatment. The ECT machine used for the study is a thymatron System IV by Somatics, LLC. The independent variable was the intake of clozapine and the dependent variable was the seizure duration. We assess the normality of the variable using the Kolmogorov-Smirnov test. The data highlighted a big amount of no convulsions. We assumed they were real as the distribution between groups was not explained by chance. We analyzed the results using the T-test. However, we also applied the nonparametric tests that confirmed our results. Secondly, we studied the seizure duration among patients receiving anticonvulsive drugs. In this case, we also studied the seizure threshold and the stimulus duration. As these variables are defined by the apparatus, we used the Mann-Whitney U test for analyzing the results.

Results

We extracted data from a sample of 11569 determinations belonging to 448 patients. The distribution between sex was unequal. There were 55,6% females and 44,4% males. The sample comprised ages from 20 to 104 years old. The median age was 60.58 years old. There were 2411 patients taking mood stabilizers and 1016 patients under clozapine treatment. We found that the duration of the seizure during ECT treatment among patients receiving clozapine was longer than in those without clozapine treatment. This difference was statistically significant (P<0,05). The longest seizure lasted for less than 2 minutes. Patients under antiepileptic treatment presented a reduced seizure compared to patient that are not taking this medication. However, the difference is not significant in neither of the tests (P=0,9). The stimulus duration was prolonged in patients receiving anticonvulsant medication compared to patients who were not taking these psychotropic drugs (P=0,001), as well as, the seizure threshold was found higher in patients treated with anticonvulsants (p<0,05).

Figure 1. Age and sex distribution of patients included in the study.

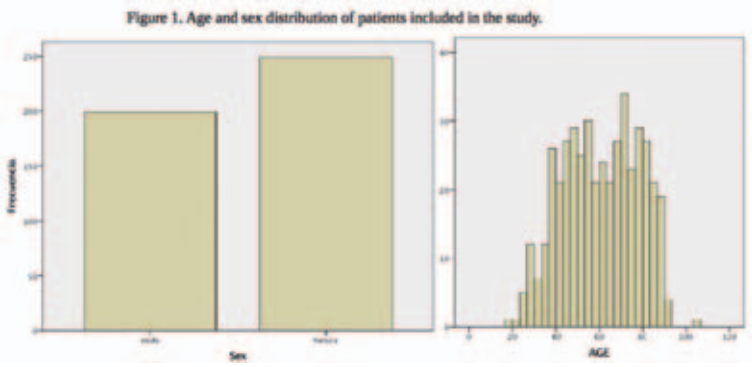

Fig 2. Duration of the convulsion in patients receiving ECT and clozapine treatment.

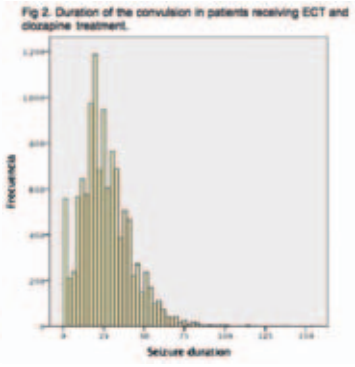

Table 1. Table of contingency of seizure duration by clozapine treatment.

Estadísticas de grupo

	Clozapine	N	Media	Desviación estándar	Media de error estándar
Seizure duration	no	10553	26.01	15,772	,154
	yes	1016	28.50	14,354	,453

Prueba de muestras independientes

		Prueba de Levene de igualdad de varianzas		prueba t para la igualdad de medias						
		F	Sig.	t	gl	Sig. (bilateral)	Diferencia de medias	Diferencia de error estándar	95% de intervalo de confianza de la diferencia Inferior	Superior
Seizure duration	Se asumen varianzas iguales	2,186	,139	-4,830	11567	,000	-2,484	,514	-3,492	-1,476
	No se asumen varianzas iguales			-5,220	1263,045	,000	-2,484	,476	-3,417	-1,550

Table 2. Duration of seizure by intaking of mood stabilizers

Estadísticas de grupo

	Mood stabilizers	N	Media	Desviación estándar	Media de error estándar
Seizure duration	No	9158	26,25	15,652	,164
	Yes	2411	26,17	15,695	,320

Prueba de muestras independientes

		Prueba de Levene de igualdad de varianzas		prueba t para la igualdad de medias						
		F	Sig.	t	gl	Sig. (bilateral)	Diferencia de medias	Diferencia de error estándar	95% de intervalo de confianza de la diferencia Inferior	Superior
Seizure duration	Se asumen varianzas iguales	3,466	,063	,212	11567	,832	,076	,359	-,627	,779
	No se asumen varianzas iguales			,211	3771,129	,833	,076	,359	-,628	,760

Table 3. Stimulus duration and seizure threshold by mood stabilizers crosstabulation.

	Mood stabilizers	N	Rango promedio	Suma de rangos
INT	No	8992	5591,07	50274922,5
	Yes	2366	6015,57	14232838,5
	Total	11358		

Estadísticos de prueba[a]

	INT
U de Mann-Whitney	9842394,50
W de Wilcoxon	50274922,5
Z	-5,627
Sig. asintótica (bilateral)	,000

	Mood stabilizers	N	Rango promedio	Suma de rangos
Stimulus duration	No	8951	5605,91	50178537,5
	Yes	2360	5845,97	13796478,5
	Total	11311		

Estadísticos de prueba[a]

	Stimulus duration
U de Mann-Whitney	10113861,5
W de Wilcoxon	50178537,5
Z	-3,217
Sig. asintótica (bilateral)	,001

Conclusions

The results confirmed our hypotheses and are consistent to the previous evidence that psychotropic drugs have an effect on ECT electrical parameters. Patients treated with clozapine presented indeed longer convulsions. However, in terms of clinical applicability the difference of means is irrelevant. Although previous studies reported some patients experiencing prolonged seizures we did not find any case in our sample. This underpins the principle that adverse effects due to the combined use of clozapine and ECT are not frequent. (6) (7) Seizure duration was not modified by anticonvulsive treatment. Although statistical significant, the changes observed in the length of the stimulus and the threshold seizure are minimum. Limitations of this article include heterogeneity of the sample regarding the sex distribution, the non-randomised design and the numerical difference between cases and controls. Furthermore, the intake of other psychotropic drugs and medical treatments was not taking into account. As well as, patients suffering from a medical condition. Considering the limitations of the study, we do not know the clinical implications of this changes and a follow-up on these patients should be done. The available guidelines on this topic are inconsistent and disregards the effects of withdrawals, as well as the benefits of preserving both treatments. We consider the individual benefit/risk should be studied although further investigation on this topic is needed for taking final conclusions.

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The authors have no conflicts of interest to disclose concerning the presentation

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