Olanzapine effects on emotional recognition in treatment refractory schizophrenics

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Efectos de la olanzapina sobre el reconocimiento emocional en esquizofrénicos refractarios al tratamiento

Summary

Introduction. *The main purpose of this study was to determine if olanzapine (OLZ) can improve the ability to recognize emotional expressions, in the facial, prosodic and contextual modalities in treatment refractory schizophrenics (TRS) and, if this could be related to its effects on depressive symptoms.*

Method. *14 TRS participated in the study. The Calgary Depression Scale and tasks for recognition of facial, prosodic and contextual emotions were applied prior to and 8 weeks after consuming OLZ. The results were compared to a control group (CO).*

Results. *TRS obtained lower scores than the CO on the recognition of facial and prosodic emotions. They also showed less empathy to the happiness film and they expressed incongruous answers on the contextual emotions. The TRS increased the number of correct responses for the prosodic recognition of happiness and they showed a reduction in their depressive symptomatology after OLZ treatment.*

Conclusions. *OLZ caused a decrease of the depressive symptoms and improved the interpretation of positive prosodic affective stimuli, an aspect that may facilitate the social adaptation of TRS.*

Key words: *Refractory schizophrenia. Olanzapine. Emotional recognition. Depression.*

Resumen

Introducción. *El objetivo principal del presente trabajo fue el determinar si la olanzapina (OLZ) puede mejorar la capacidad para reconocer expresiones emocionales en las modalidades facial, prosódica y contextual de pacientes esquizofrénicos refractarios (ERT) y si ello pudiera tener relación con su efecto sobre síntomas depresivos.*

Método. *Participaron 14 ERT a quienes se les aplicaron antes y después de 8 semanas de consumir OLZ la Escala de Calgary de Depresión y las tareas de reconocimiento de emociones faciales, prosódicas y contextuales. Los resultados fueron comparados con un grupo control (CO).*

Resultados. *Los ERT obtuvieron menores puntajes que los CO ante el reconocimiento de emociones faciales y prosódicas; asimismo mostraron menor empatía ante la película de alegría y expresaron respuestas incongruentes ante las emociones contextuales. Los ERT incrementaron el número de aciertos para el reconocimiento prosódico de alegría y disminuyeron su sintomatología depresiva después del tratamiento con OLZ.*

Conclusiones. *La OLZ causó una disminución de los síntomas depresivos y mejoró la interpretación de estímulos afectivos prosódicos positivos, condición que podría facilitar la adaptación social en los ERT.*

Palabras clave: *Esquizofrenia refractaria. Olanzapina. Reconocimiento emocional. Depresión.*

INTRODUCTION

In recent years, interest in the study of emotional disorders of the schizophrenics has been renewed, since these have a considerable repercussion on interpersonal relationships as well as on adaptation to the environmental setting and, thus, on the quality of life of these patients[1]. There is evidence that schizophrenics present deficits in the decoding of emotional facial expressions and mistakes in their verbal description as well as alterations in emotional states and their expression[2-6]. Other studies have demonstrated that these patients find it difficult to identify prosodic emotional aspects and frequently make mistakes in social judgement as they cannot give adequate significance to interpersonal situations[7,8]. Furthermore, it has been proposed that there is a dissociation between perceptual, experiential and expressive aspects of emotion in schizophrenia[9,10]. Given the importance of having adequate recognition of emotional expressions in social functioning of schizophrenics, its study and the possible effects of drug treatments on the emotional processes acquire relevance.

On the other hand, recent studies have manifested that the new drugs, called atypical neuroleptics, for the treatment of schizophrenic signs and symptoms, not

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only generate improvement in the positive and negative symptoms of these patients but also on some cognitive functions[11,12]. In addition, it has been described that at least one atypical drug, risperidone, has produced improvement in emotional perception tasks in treatment refractory patients[13].

Olanzapine (OLZ) stands out among the atypical drugs since, besides having a greater efficacy spectrum, greater effectivity in the treatment of patients resistant to conventional treatments and a lower incidence of side effects than the typical antipsychotics, as occurs with other atypical antipsychotic drugs, it does not generate agranulocytosis, which represents an important risk during treatment with clozapine, the first atypical neuroleptic[14]. Cuesta, Peralta and Zarzuela[11] found that OLZ was more effective than risperidone and that typical neuroleptics in the treatment of negative symptoms additionally generated an improvement in the attention processes. Purdon[15], found similar effects of OLZ on immediate memory processes and visual recognition. Romera and Gurpegui[16] reported that a group of patients treated with atypical antipsychotics (OLZ or risperidone) showed greater visual memory abilities than those treated with the typical ones. Furthermore, OLZ has been shown to have an important effect on depressive symptoms that are commonly present in schizophrenia[14,17].

Atypical neuroleptics have had great importance in the treatment of schizophrenic patients resistant to treatment with typical neuroleptics (TRS). These patients persistently show positive and negative symptoms and represent about 30% of the schizophrenic population[18]. In previous investigations in this subgroup of schizophrenics, greater deficits were found in the recognition of emotional facial expression than in those patients who respond to typical treatment, although it was correlated with the typical neuroleptic dose[19]. Equally, Joober et al.[20] found significant differences between responders and non-responders in logical-verbal memory and associative learning tasks, with less efficiency in the TRS. Furthermore, the functional organization of the brain, evaluated by cerebral activity, shows differences in these resistant patients in comparison to the non-resistant ones[21].

Thus, given that OLZ has been useful in the treatment of resistant schizophrenia and has shown to have an effect on cognitive processes as well as on visual recognition and depressive symptoms, the objective of this study was to determine if this drug can improve ability to recognize emotional expressions in the facial, prosodic and contextual modalities of treatment refractory schizophrenic patients and if it could have a relationship with its antidepressive effect.

METHOD

Subjects

A total of 14 TRS male patients selected from the out-patient clinic of the Community Center of Mental Health No. 1, Mexican Institution of Social Security (IMSS), Jalisco participated in the experiment. The patients were diagnosed by two experienced psychiatrists as paranoid schizophrenics based on the international criteria of DSM-IV in force[22] and of the ICD-10[23]. To do so, the Brief Psychiatric Rating Scale[24] and the Positive and Negative Symptoms Scale[25] were applied. Furthermore, the patients fulfilled the Keefe, Mohs and Silverman[26] criteria of treatment refractory schizophrenia. A control group of healthy subjects (CO) was used. They were paired according to age (between 21 and 42 years), schooling (minimum of 9 years), gender (male) and right-handed preference, and evaluated through the Annet's test[27]. Those patients who presented another type of comorbid neurological or psychiatric disorder or who consumed any type of drug were not included in the sample. Thus, those subjects with a background of any type of addiction, mental disease, central nervous system pathology or who were under psychopharmacological treatment were not included in the control group. All the participants were informed on the procedure and gave their written consent.

Pharmacotherapy

The patients initially received typical neuroleptics (haloperidol and/or fluphenazine decanaote) and a drug to correct extrapyramidal symptoms (biperiden). In the condition prior to the intake of olanzapine, there was a one-week wash-out phase for haloperidol and a one month one for fluphenazine decanaote, in order to establish a single treatment with OLZ. From the first to the fourth week, a 10 mg dose was administered and from the fifth to the eighth week, one of 20 mg every 24 hours. These criteria were uniformly applied to all the patients.

Procedure

The patients were assessed in two sessions, pre-treatment, under typical neuroleptic based treatment, and post-treatment, after 8 weeks of having initiated treatment with OLZ. The control group also attended two sessions, with an inter-evaluation period of 8 weeks, in order to estimate the possible learning effects. The approximate duration of each session was 2 hours and they carried out between 10 a.m. and 2 p.m.

The tasks were applied to both patients as well as to the control group in a counterbalanced way during both sessions.

The Calgary scale to assess depression in schizophrenia

This scale was especially designed to determine depressive symptoms in schizophrenic patients[28].

Prosodic emotion identification test

It was performed by presenting a recording of 32 sentences selected from a study designed to test the utility

of the stimuli. These stimuli had a neutral semantic content from the emotional point of view and were expressed by two experienced speakers (a man and a woman) who pronounced them with different affective, that are happy, sad, angry and fearful tones. The stimuli were randomly presented to the subjects. The subjects were requested to report the emotional tone expressed in the sentences. To do so, they were given a list with the four possible emotions. The answers were recorded by the experimenter to determine the number of correct answers and errors.

Facial emotion identification test

Ekman and Friesen stimuli[29] were applied and presented on a 15 inch screen of a personal computer. Each subject was sitting at a distance of 60 cm while several photographs of the face of 10 persons (five men and five women) with Latin American racial features appeared. Each model presented six basic emotions (happiness, sadness, anger, fear, surprise and disgust) and an emotionally neutral expression. The subjects should mention the emotion, which in their opinion, each stimulus represented and then press a key. For this, they were also given a list with the possible emotional expressions represented in the photographs. This test had no time limit and the answers were written down by the experimenter to determine the number of correct answers and errors as well as the approximate time that it took the subjects to respond.

Identification of emotions within a context test

Four video tapes were presented with an approximate duration of 2 minutes. All of them were presented in the Spanish language, without music, with several characters, in which a dialogue was established and there were representative situtations for each one of the four emotions (happiness, sadness, anger and fear). These were reproduced by a video cassette and projected on a 17 inch computer screen. Each subject was sitting at a distance of 1.5 m while watching the stimuli, the same that were presented randomly among the subjects. After, the subject was requested to respond to a questionnaire that determined his ability to describe the scene in a general way, identify the emotions expressed by the principal and secondary characters as well as the intensity perceived with which the characters experienced the emotion. In addition, the subject had to indicate the emotion that he experienced on watching each on the video taps and in what intensity.

Statistical analysis

Non-parametric tests were performed with the scores of the psychiatric scales obtained by the patients (BPRS and positive and negative PANSS), as well as with the number of correct answers and errors in the tasks for both groups. To assess the differences between the pre and post-treatment sessions, the Wilcoxon test was used for each group, independently. The Mann-Whitney U test was applied for comparison between groups. A Pearson's correlation analysis was also performed between the parameters obtained in the different tasks and the scores found on the depression scale. The chi-squared test was also used to analyze the number of congruent and incongruent answers of the responses emitted by both groups in the contextual emotion tasks.

RESULTS

OLZ caused a 49% ($p = 0{,}008$) reduction in the BPRS scores and a 33% ($p = 0{,}008$) and a 26% ($p = 0{,}01$) in the scores of the positive and negative symptoms scales of PANSS, respectively, in the TRS patients.

Depression scale

A significant decrease was found in regarding, the scores obtained by the patients on the Calgary scale when comparing pre and post-treatment conditions ($p = 0{,}01$), and this correlated with the intensity of the empathy reported by the patients on seeing the pictures that contain emotional representations of anger and sadness ($r = 0.50$) during the pre-treatment phase (fig. 1).

Prosodic emotion identification test

A significant difference was identified between the number of correct answers in the recognition of emotional prosody obtained by the control group in comparison with the patient group ($p = 0.02$). When a specific analysis by emotion was performed, we found significant

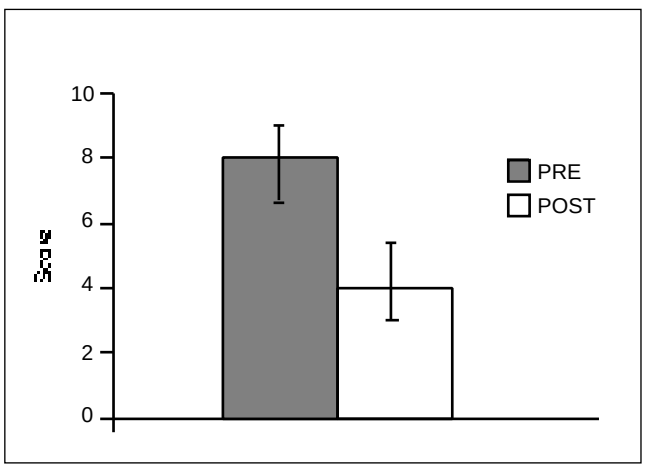

Figure 1. Mean and standard errors of the scores of the Calgary Scale of depression before and after treatment with olanzapine.

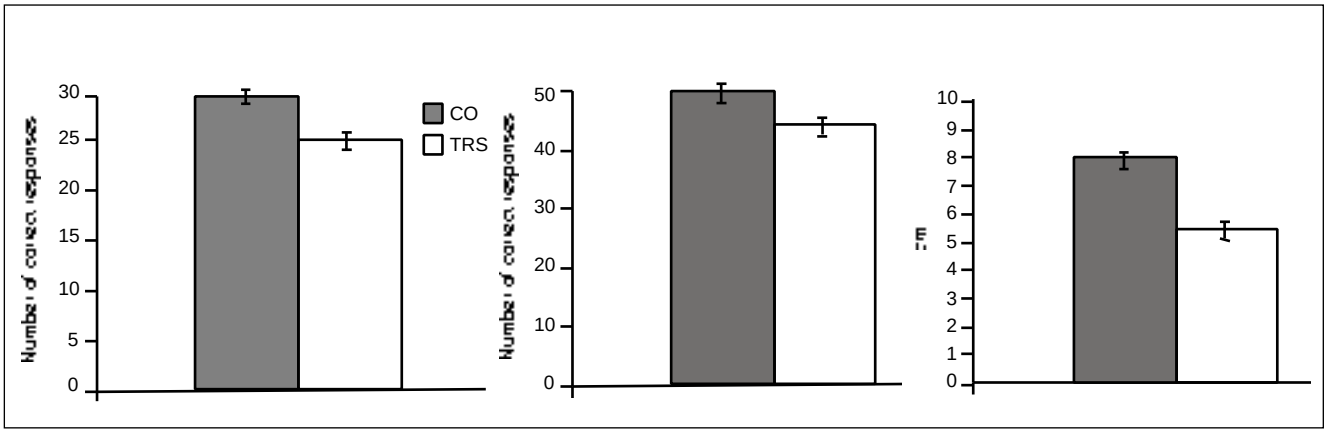

Figure 2. Differences between the control group (CO) and treatment refractory schizophrenics (TRS) in the recognition of prosodic and facial emotions as well as the intensity to experience empathy of happiness. (Means and standard errors).

differences between controls and patients in pre-treatment phase to the happiness and sadness stimuli (p = 0.009 and p = 0.006, respectively). A significant improvement was also observed in the patient group for the identification of prosodic stimuli of happiness after olanzapine intake (p = 0.008) (fig. 2).

Facial emotion identification test

Significant differences were found on comparing the performance of the patients with the control group in the identification of emotional facial expressions (p = 0.03) (fig. 2). In the specific analysis of each emotion, differences are seen between groups for the identification of disgust stimulus in the pre-treatment phase (p = 0.04). There are no differences between groups when response times to these stimuli are assessed; however, the control group could improve both the response rate as well as the number of correct answers obtained (p = 0.02) from the first to the second session (p = 0.05), which was not observed in the TRS. No significant differences were observed for treatment with OLZ.

Test of identification of emotions within a context

We found significant differences between groups in regard to the intensity of the emotion perceived expressed by secondary characters in pictures of happiness and anger (p = 0.009 and p = 0.04, respectively), this being less in the patients. We also found differences between groups in relation to the emotion caused by the happiness picture, with less magnitude experienced by the patient group (p = 0.05). In general, we found that most of the patients could identify the emotion represented in the pictures selected. However, when analyzing the type of response expressed, we found a greater number of incongruent verbalizations in the patients in comparison with the control group when seeing the pictures representing fear (p = 0.004), happiness (p = 0.02) and sadness (p = 0.002) (fig. 3). Equally, some patients

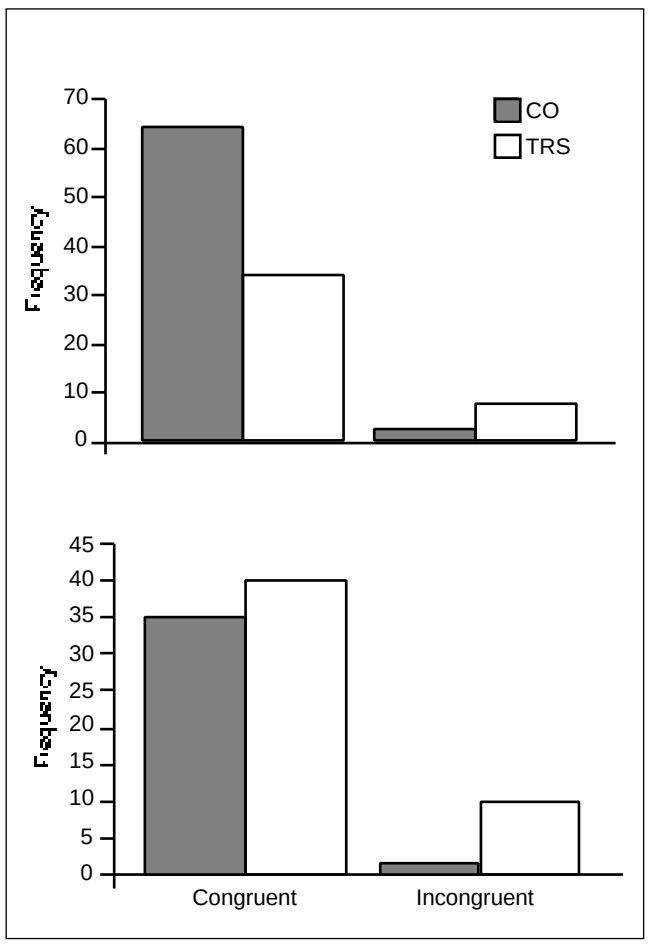

Figure 3. Frequency of congruent and incongruent answers expressed by the control group (CO) and treatment refractory schizophrenic patients (TRS) to pictures of fear and sadness.

mentioned that they felt no emotion when seeing the pictures of sadness, fear and happiness, an aspect in which the control group differed significantly. Finally, no differences were found in regards to the type of response experienced by the patients between the pre and post-treatment sessions.

DISCUSSION

The results of the present study showed that the 8 week treatment with olanzapine caused better performance in the recognition of prosodic expression of happiness, besides a significant decrease in the depressive symptoms of the patients, which coincided with that observed in other studies[14,17]. It could also be observed that the depression scores correlated with intensity of the empathy reported by the patients on seeing scenes representing anger and sadness in the pre-treatment phase, that is, the greater the depressive symptoms, the greater the ability to empathized with these emotions. No consistent effect of OLZ on the recognition of other prosodic or facial emotions was observed. These results suggest that OLZ, instead of having an effect on the specific mechanisms of emotional recognition, because it improves mood state (depressive) of the patient, it could be facilitating the identification of emotional expressions congruent with this state, thus improving the recognition of the happiness prosody.

Another possibility would be that the improvement of the positive and/or negative symptoms after treatment would be related to the improvement in the recognition of the prosody of happiness. However, if the improvement in the positive symptoms such as hallucinations, delusions or suspiciousness had any relationship with the improvement in emotional recognition, a more global effect could be expected on the recognition of the different emotions (happiness, sadness, anger, etc.), both facial as well as prosodic, and not an exclusive effect on the prosody of happiness. Kohler et al.[30], in an investigation related to alterations in emotional recognition, the psychopatology and cognition in schizophrenia, point out that emotional recognition has a certain independence from the negative symptoms and that they do not necessarily relate to the affective disorders and psychosocial functioning, since they did not find a correlation between the deficit in emotional recognition and negative symptoms such as emotional blunting, avolition or anhedonia. On the other hand, Neither Shaw[31] found a correlation between the performance in emotional or prosodic recognition with the psychiatric symptoms in schizophrenic patients. However, in another investigation, Shaw et al.[32] observed a negative correlation between inappropriate affect and facial recognition. Considering the findings obtained up to now, it is not possible to define a clear relationship between the changes in ability to recognize emotions and symptoms, whether positive or negative.

Part of the effects of OLZ on depressive symptoms seems to be due to the extracellular increase of dopamine and noradrenaline on the prefrontal cortex, besides serotonin, the effect of whith strengthened with the joint administration of fluoxetine[14,33,34]. These neurotransmitters are involved in the regulation exercised by the prefrontal cortex on the cortical and subcortical limbic structures related to the mood state[35].

On the other hand, the TRS, in comparison to the control group, had a lower amount of correct answers on the facial and prosodic expressions recognition tasks, less empathy to the happiness pictures, as well as a greater amount of incongruent responses in the evaluation of emotions expressed within a social context. On performing a specific analysis for each emotion represented, significant differences were observed between groups to the prosodic stimuli of sadness and happiness, as well as to the facial stimulus representing disgust, with lower points in the TRS.

Other authors[2-6,36] have reported similar results regarding to the recognition of facial emotions in patients with schizophrenia, mentioning that mistakes in the identification of these stimuli vary according to the type of emotion represented. This would probably explain the number of errors obtained by the TRS only for the facial representation of disgust. It is important to mention that, in this study, the tasks were applied without a time limit. This could explain why the mistakes do not seem as severe, as would be expected, in the TRS when compared to the control group, since it has been observed that the performance of these patients in the recognition of facial expression of happiness is significantly less than of the non-resistant and controls, when they should respond within a certain time[19].

Our results suggest that the TRS patients probably present a dysfunction in the cerebral structures related to the identification and assignation of emotional significance to stimuli from the environment setting, as are the amygdala and the temporal, cingulated and prefrontal cortices [37-41].

On the other hand, Edwards et al.[7] found significant alterations in a group of schizophrenics when they should recognize prosodic stimuli of sadness and fear. These authors mentions that these mistakes were stable both in the acute phase as well as the disease remission phase and that they were present even from the first psychotic episode. They proposed the notion that a dysfunction in the basolateral amygdala could be considered as a trait marker for this disease. Other evidence mentions that the cognitive and social deficits in the schizophrenics can be detected from childhood, and that these present a progressive deviation with age that becomes clearly in early adolescence[42].

Significant differences were found between groups in regard to the number of incongruent answers. In this regard, it should be mentioned that, in agreement with the studies of Kington, Jones and Hopkin[4] and Poole, Tobias and Vinogradov[8], it is possible that the schizophrenic patient not only has defects related with the primary

identification of emotional stimuli but also that, there exists an alteration in the level of posterior cognitive processing which is thus more complex and integrative, in which the executive processes would basically participate on the prefrontal cortex level. That is, although the patients may perceive the emotions in a more or less adequate form, it is difficult for them to interpret them and to generate judgements based on this type of information, acting with errors to give a congruent response with the stimulus received.

The control group increased the number of correct answers and decreased their response time to facial emotional expressions in the second session, which suggests a learning effect that was not found in the TRS. The importance of dedicating training for the interpretation of the social keys to the patients with TRS in addition to drug treatment can be emphasized, since although this drug was shown to have an action on the depressive symptoms, it does not seem to have effects on the emotional recognition process.

In summary, our results suggest that there is a decrease in the ability to value and interpret emotional stimuli on both the facial as well as prosodic level in TRS patients in comparison to the normal subjects as well as a limitation in the elaboration of social judgements related with the emotions perceived within a context. Olanzapine caused a clear improvement of the depressive symptoms of the patients, which could also be facilitating the identification of prosodic stimuli of happiness, according to with the emotional tone. The previous, together with the reduction of the psychopathology, could affect the ability of the patients to adapt to their social setting, and therefore, on their quality of life.

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